

# Cefiderocol

**Antimicrobial Drugs Advisory Committee Meeting  
October 16, 2019**

# Introduction to the Cefiderocol Program

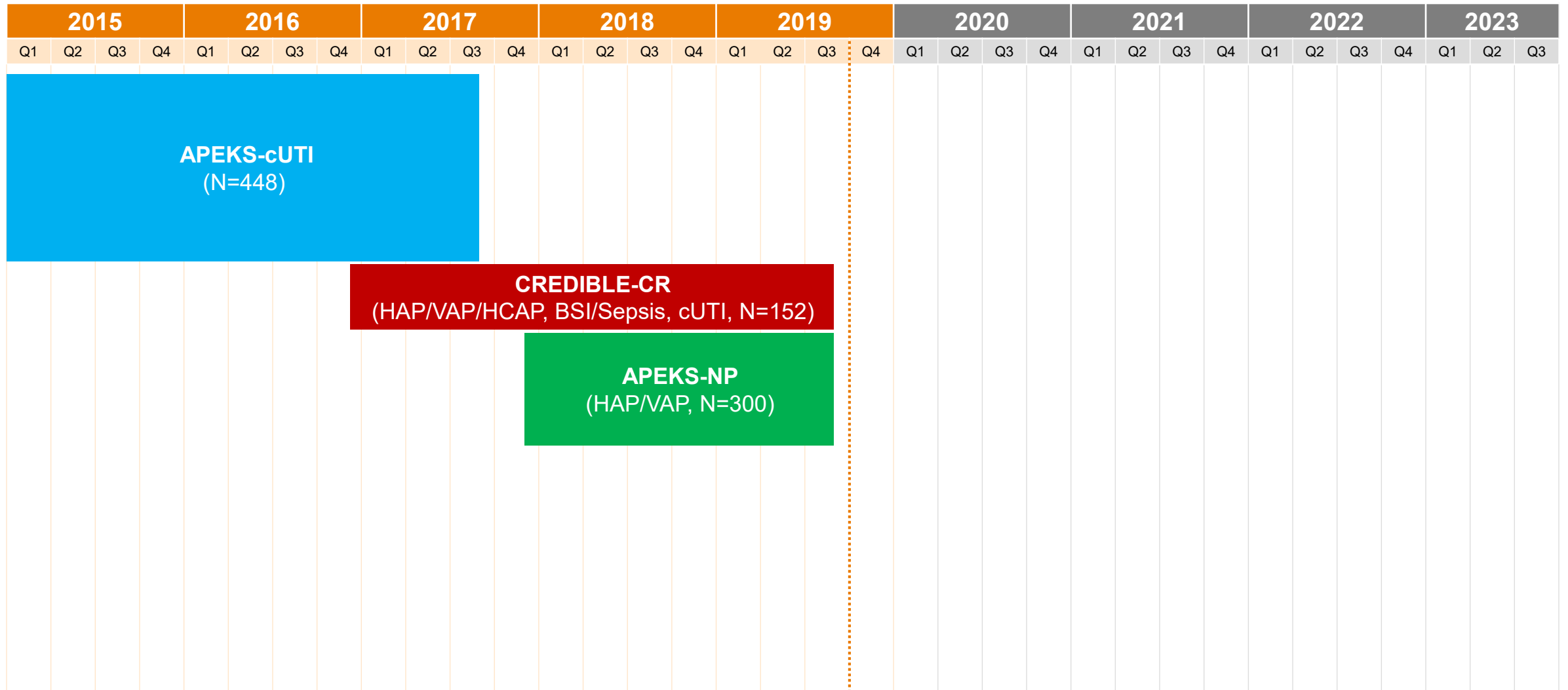
**Tsutae (Den) Nagata, MD, PhD, FFPM**

Chief Medical Officer  
Shionogi & Co., Ltd.

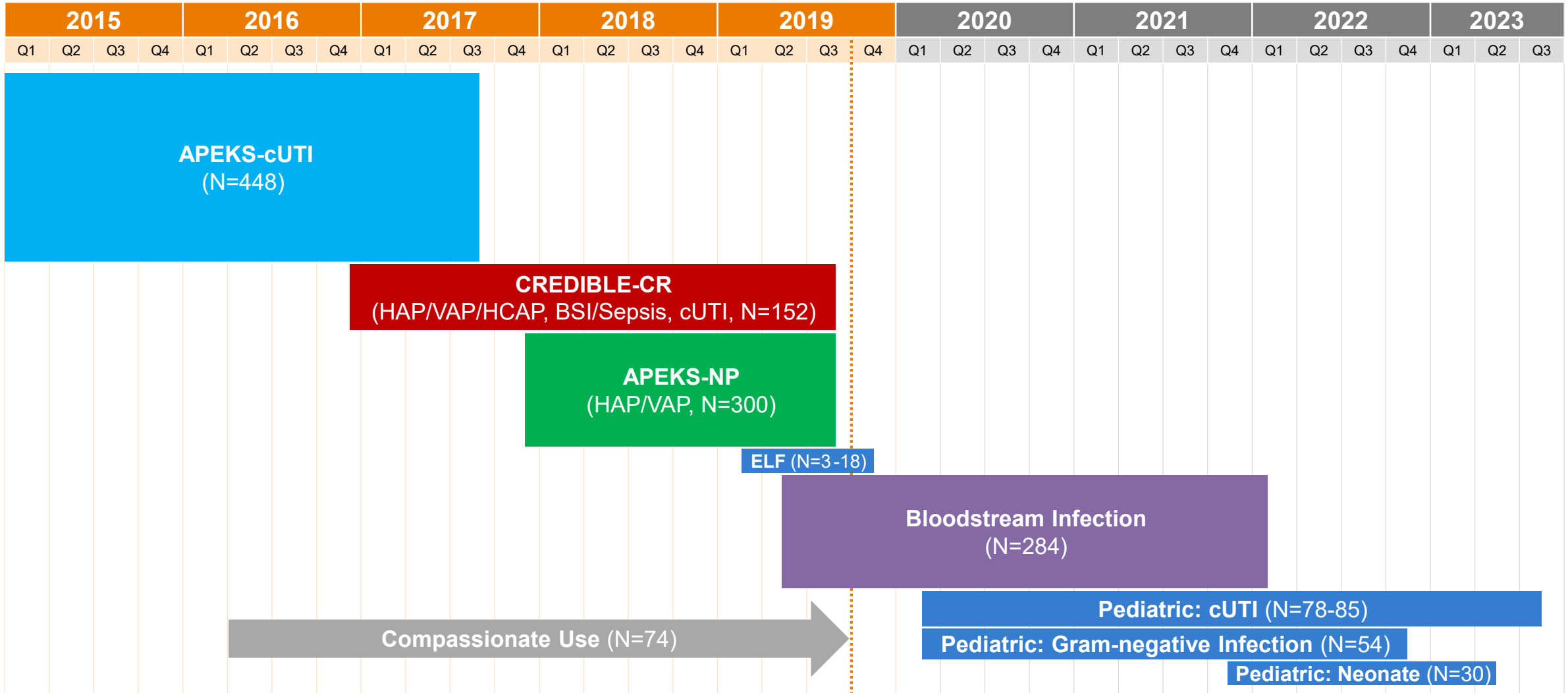
# Streamlined Development

- **Qualified Infectious Disease Product (QIDP) designation for serious infections**
- **Streamlined development**
  - Single pivotal study
  - Serious infections
  - Supported by extensive preclinical efficacy and PK/PD analyses
  - Limited-use indication
- **cUTI study**
  - Patients at risk for MDR pathogens
  - High-dose imipenem as comparator
  - Non-inferiority study design
  - Superiority post hoc

# Completed Phase 3 Studies



# Planned and Ongoing Studies



ELF=epithelial lining fluid

# cUTI Limited Use Indication

- **For the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, in adult patients caused by Gram-negative pathogens**
- **As only limited clinical safety and efficacy data are available, cefiderocol should be used to treat infections where limited or no alternative treatment options are available**
- **Recommended dose**
  - 2 grams administered every 8 hours by IV over 3 hours
  - Adjustments to dose and/or frequency of administration are recommended for patients with augmented or impaired renal function

# Agenda

<b>Introduction to the Cefiderocol Program</b>	<b>Tsutae Den Nagata, MD, PhD, FFPM</b> Chief Medical Officer Shionogi & Co., Ltd.
<b>Medical Need</b>	<b>George H. Karam, MD, MACP</b> Paula Garvey Manship Chair of Medicine Louisiana State University School of Medicine, New Orleans
<b>Microbiology and Clinical Pharmacology of Cefiderocol</b>	<b>Roger Echols, MD, FIDSA</b> Clinical Development Shionogi Inc.
<b>cUTI Study – Efficacy and Safety</b>	<b>Simon Portsmouth, MD, FRCP</b> Executive Medical Director, Medical Science Shionogi Inc.
<b>Other Cefiderocol Studies and Mortality Assessment</b>	
<b>Benefit/Risk of Cefiderocol for cUTI</b>	<b>David Paterson, MBBS, PhD, FRACP, FRCPA</b> Infectious Diseases Physician, Royal Brisbane and Women's Hospital Professor of Medicine, University of Queensland, Australia

# Medical Need

**George H. Karam, MD, MACP**

Paula Garvey Manship Chair of Medicine

Louisiana State University School of Medicine, New Orleans

# Definition of Complicated Urinary Tract Infections

- **Uncomplicated urinary tract infection**
  - Infection in a structurally and neurologically normal urinary tract
- **Complicated urinary tract infection**
  - Infection in the presence of factors that predispose to persistent or relapsing infection
    - Foreign bodies (calculi, indwelling catheters, or other drainage devices)
    - Obstruction
    - Immunosuppression
    - Renal failure
    - Renal transplantation
    - Urinary retention from neurologic disease
    - Infection in men, pregnant women, children, and patients who are hospitalized or in healthcare-associated settings

# Disease Burden of cUTI

- **3 million complicated UTIs treated in hospital setting annually<sup>1</sup>**
- **400,000 hospitalizations each year in US<sup>2</sup>**
- **50% increased incidence over past 15 years<sup>2</sup>**
- **85% are caused by Gram-negative pathogens<sup>1</sup>**
- **cUTI causes 10-30% of severe sepsis<sup>3</sup>**
  - Mortality rate of  $\geq 25\%$
- **Carbapenem-resistant Gram-negative pathogens associated with increased mortality<sup>4</sup>**

1. Flores-Mireles AL et al. *Nat Rev Micro* 2015;13:269-284.

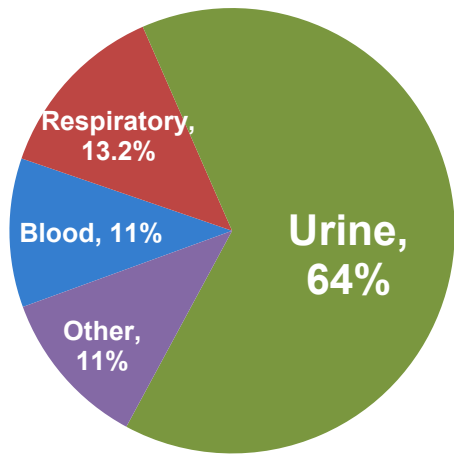
2. Simmering JE et al. *Open For Inf Dis* 2016 DOI:10.1093/ofid/ofw281.

3. Peach BC et al. *Gerontol Geriatric Med* 2016 [link.springer.com/chapter/10.1007/978-3-319-68276](http://link.springer.com/chapter/10.1007/978-3-319-68276).

4. Zilberberg M et al. *BMC Infect Dis* 2017;17:279 DOI 10.1186/s12879-017-2383-z.

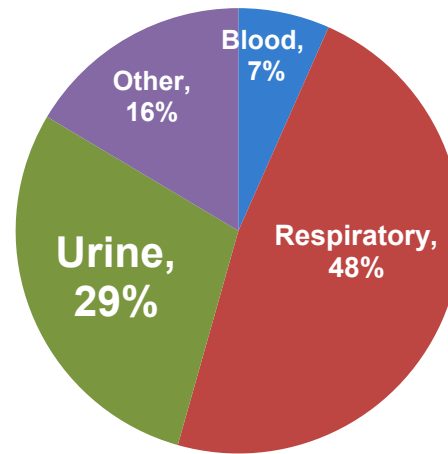
# Carbapenem-resistant Gram-negatives in cUTI (A Sampling of 180 Premier Healthcare Hospitals)

**GN Pathogens by  
Infection Site  
(Total N=510,582)**

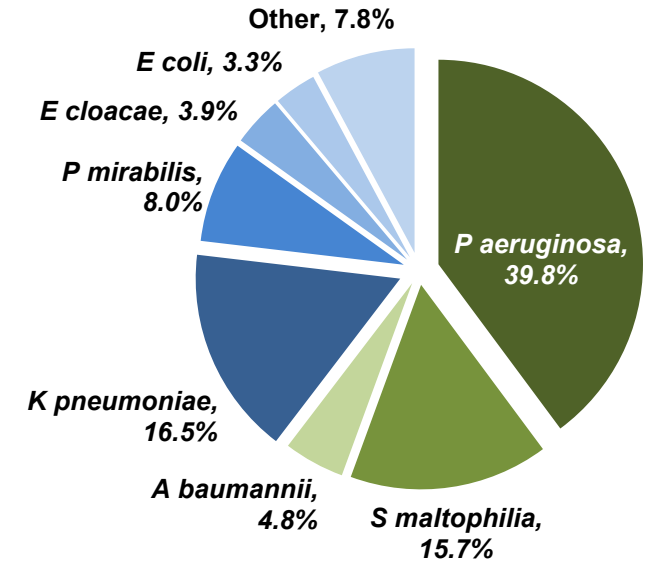


**Overall CR  
Rate  
6.7%**

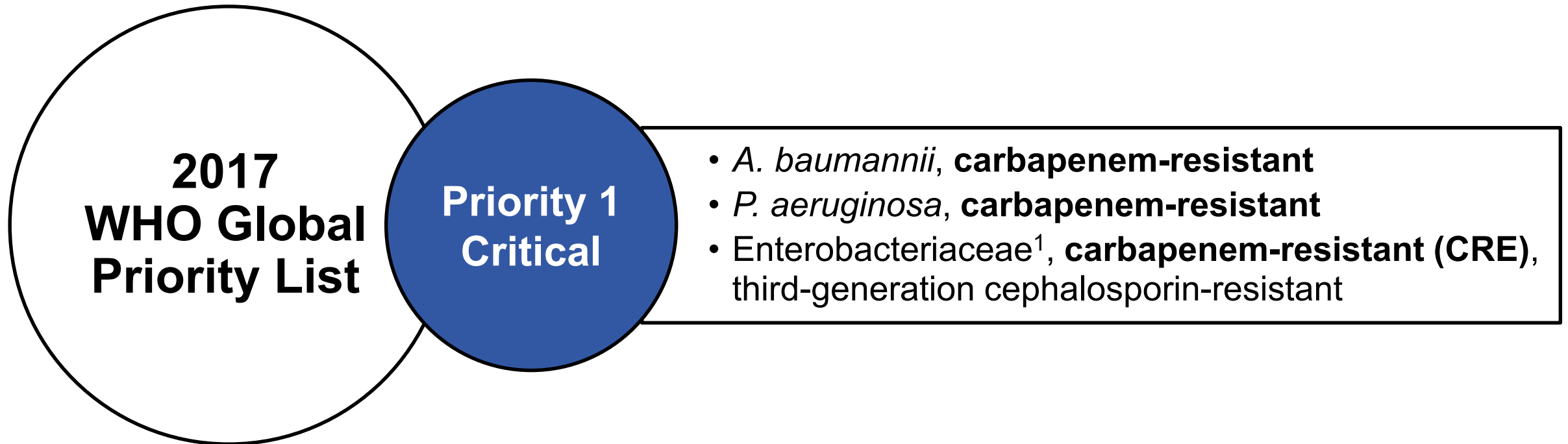
**Distribution of CR  
by Infection Site  
(CR N=34,408)**



**CR from Urine  
Non-fermenters  
60%**

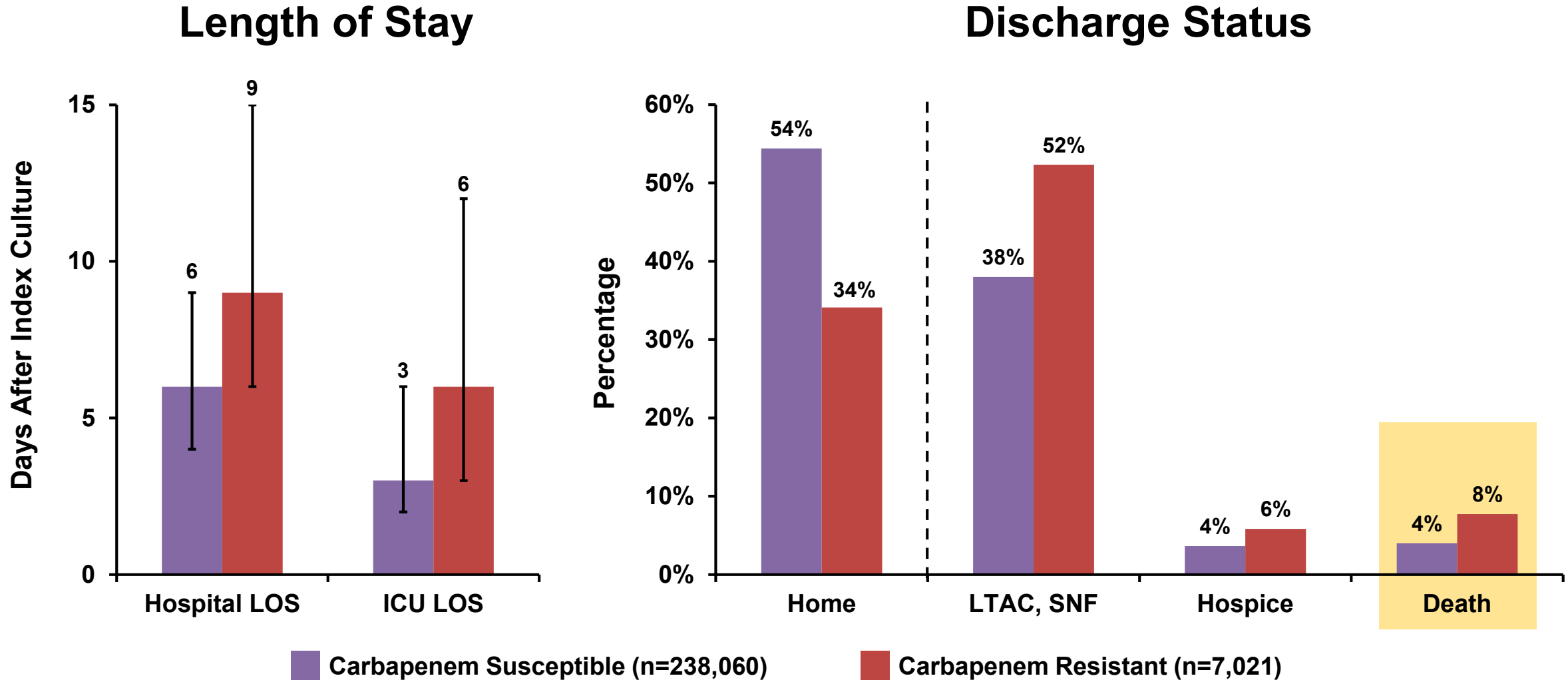


# Antimicrobial Resistance: WHO Priority Pathogens



1. Enterobacteriaceae include: *K. pneumoniae*, *E. coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp., and *Morganella* spp.

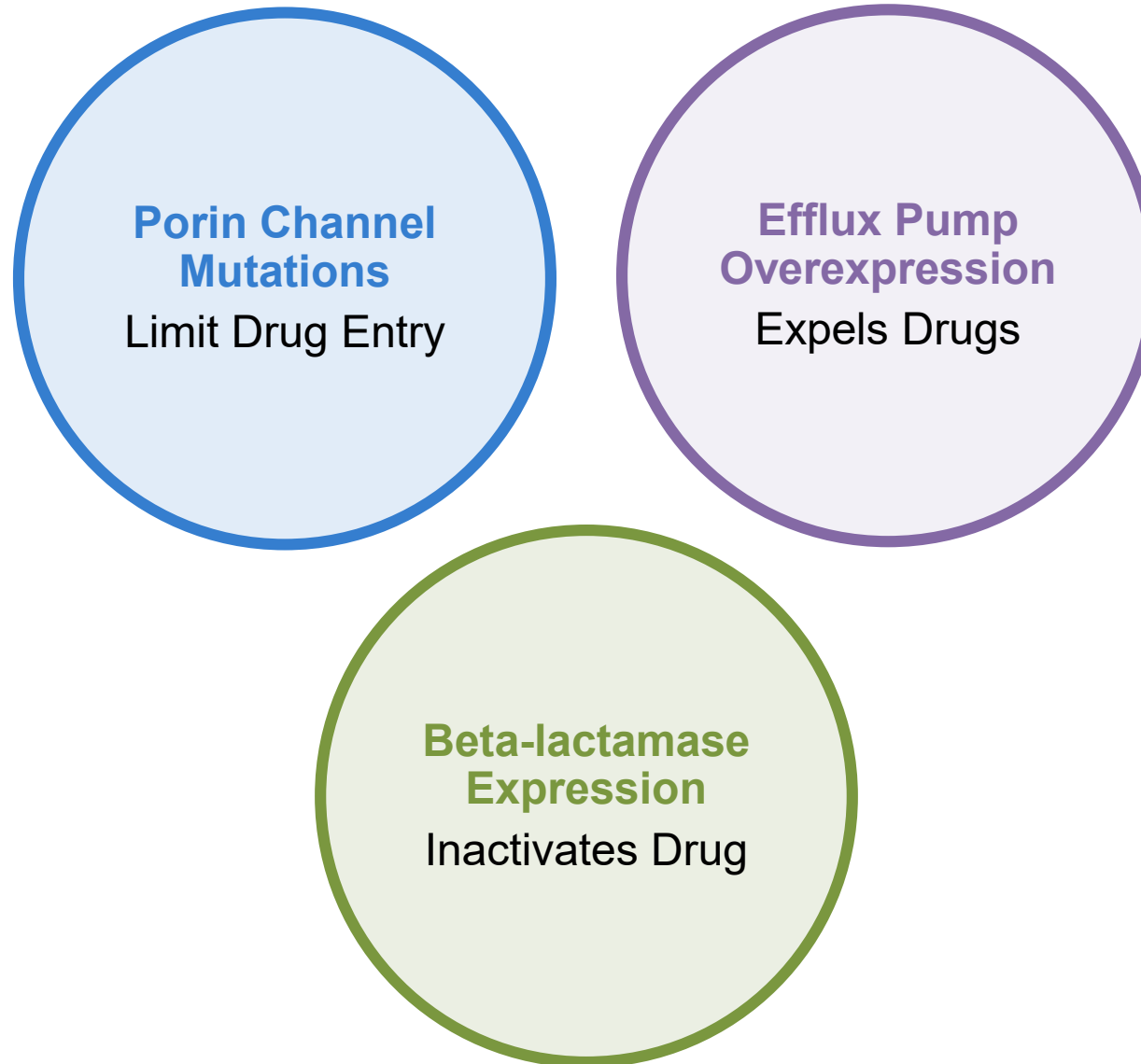
# Impact of Carbapenem Resistance on Outcomes in cUTI (N=245,081)



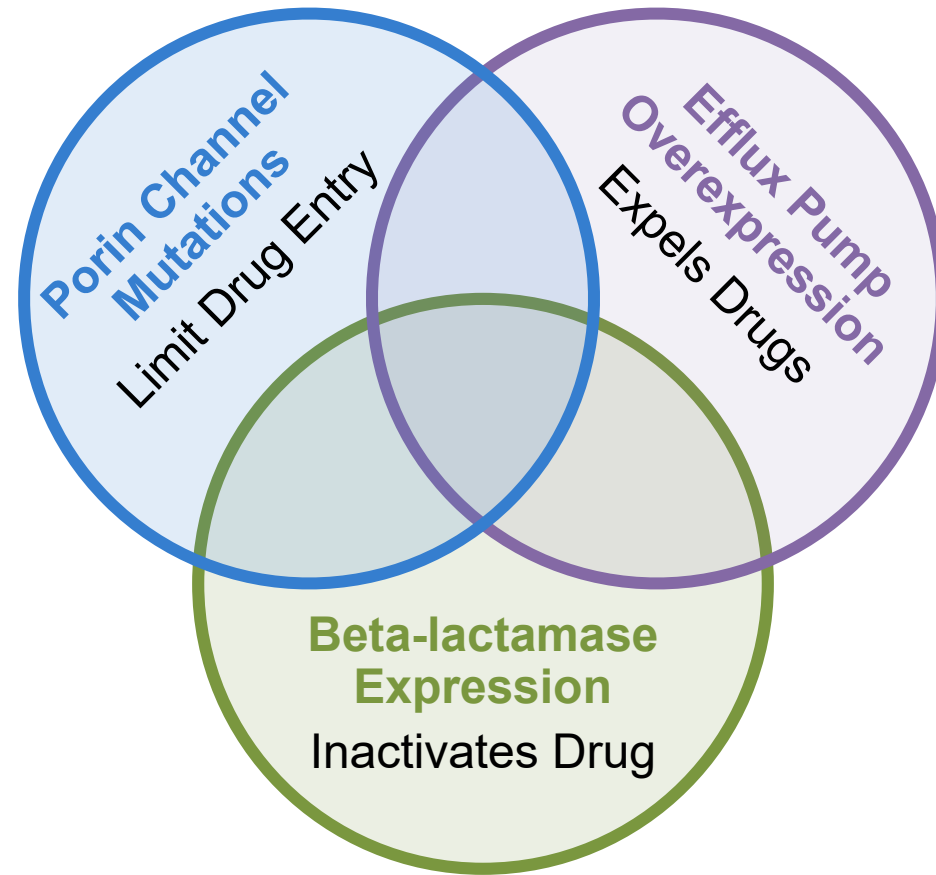
# Impact of Delayed Appropriate Therapy on Mortality in Patients with cUTI due to Carbapenem-resistant Enterobacteriaceae

- **Premier Hospital Database from July 2011-September 2014**
- **50,069 patients admitted during study period**
- **52.6% (26,336) with cUTI**
  - 0.9% with CRE
- **Delayed appropriate therapy an important driver of mortality**

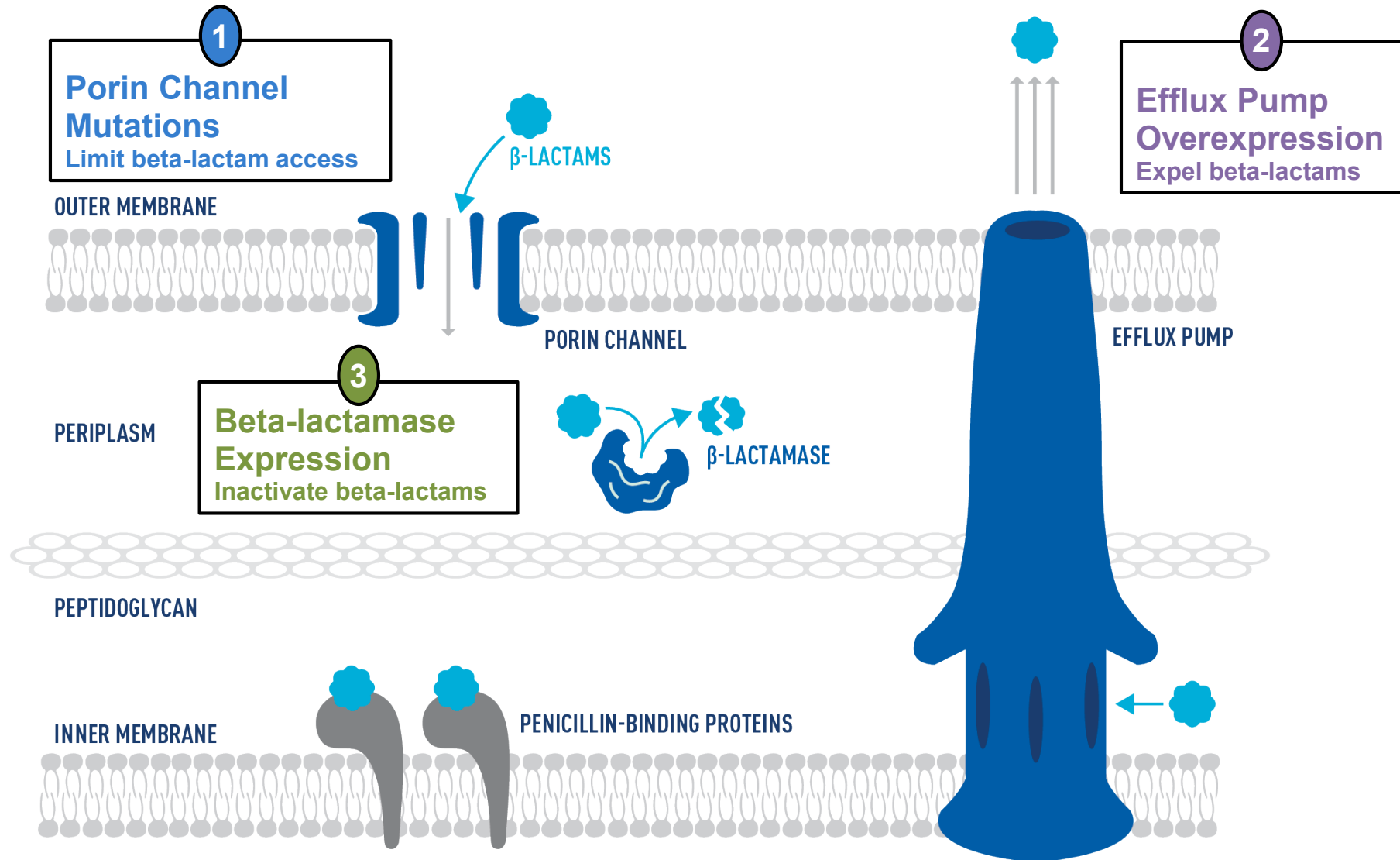
# Beta-lactam Resistance in Gram-negative Pathogens



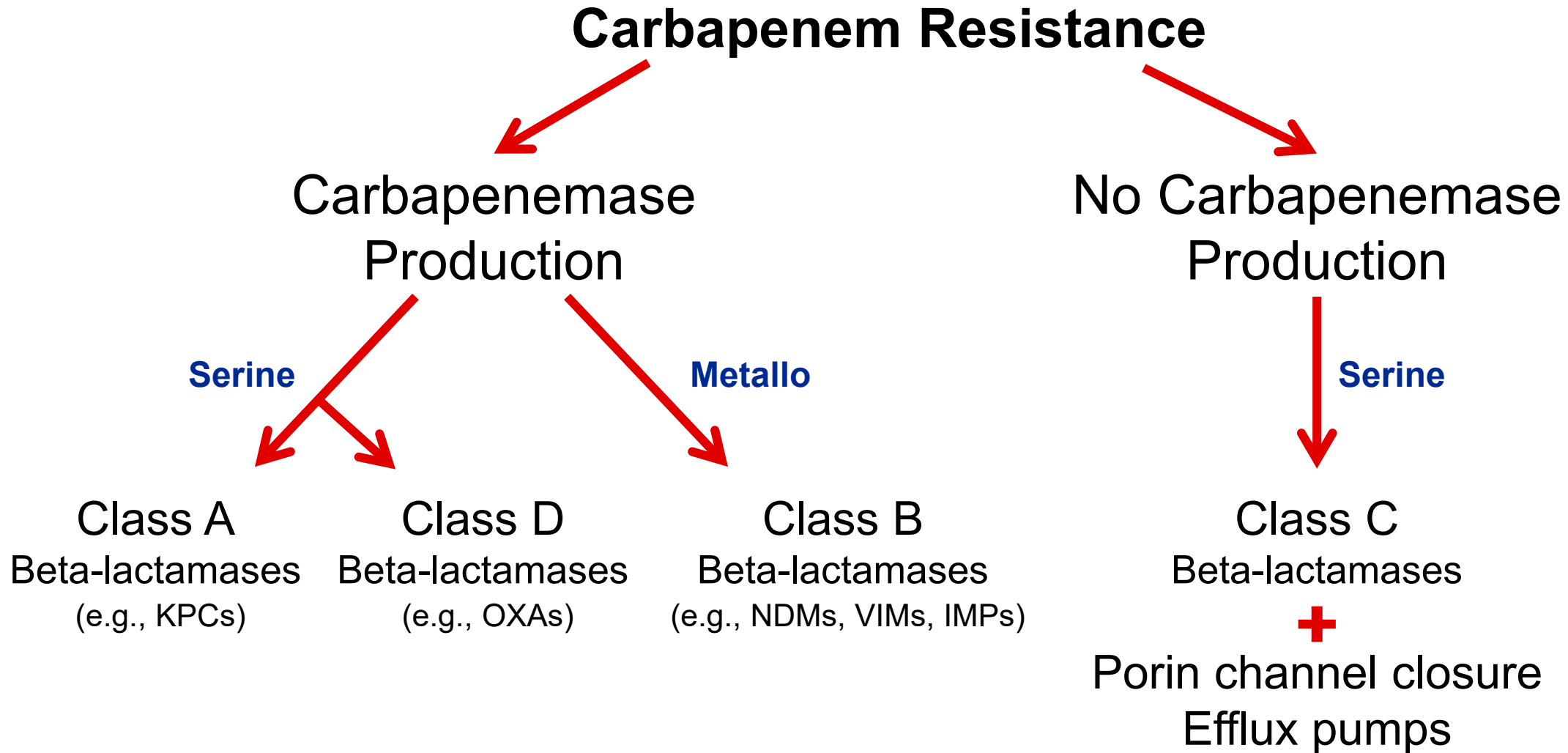
# Beta-lactam Resistance in Gram-negative Pathogens



# Beta-lactam Resistance Mechanisms



# Concept Map for Carbapenem Resistance



# History of Antibiotics for Resistant Gram-negative Pathogens

<b>1960s</b>	<ul style="list-style-type: none"><li>• Polymyxins approved</li></ul>
<b>1970s</b>	<ul style="list-style-type: none"><li>• Polymyxins “shelved” due to nephrotoxicity and neurotoxicity issues</li></ul>
<b>1980s</b>	<ul style="list-style-type: none"><li>• Aminoglycosides introduced but have toxicity risks</li></ul>
<b>1980s</b>	<ul style="list-style-type: none"><li>• Third-generation cephalosporins, fluoroquinolones, and carbapenems approved</li></ul>
<b>1980s/ 1990s</b>	<ul style="list-style-type: none"><li>• Resistance to third-generation cephalosporins and fluoroquinolones emerged, resulting in increased carbapenem use</li></ul>
<b>2000s</b>	<ul style="list-style-type: none"><li>• Carbapenem resistance emerged among Enterobacteriaceae</li></ul>
<b>2010s</b>	<ul style="list-style-type: none"><li>• Colistin returned due to lack of options, despite toxicity</li><li>• Resistance emerging</li></ul>

# Gaps in Current Therapies

- **Newer therapies do not consistently cover all beta-lactam resistance mechanisms**
  - No reliable activity against efflux pump or porin channel mutation resistance
  - No activity against any of the metallo carbapenemases
  - No activity against many of the OXA enzymes
  - *Stenotrophomonas* is intrinsically resistant to beta-lactams
- **Eravacycline: Inadequate concentration in urine**
- **Polymyxins have nephrotoxicity and resistance is emerging**

# Susceptibility of Carbapenem Non-Susceptible Clinical Isolates (SIDERO-WT 2014 to 2016 Studies)

Species (Number of Strains)	Susceptibility Percentage (%)			
	CAZ/AVI (MIC ≤8)	CEF/TAZ (MIC ≤2 or 4)	CPFX (MIC ≤1)	CST (MIC ≤2)
All Gram-negative (1873)	90.20	84.28	72.93	95.49
CarbNS Enterobacteriaceae (1021)	77.67	8.40	13.91	75.55
CarbNS non-fermenters (828)	40.96	34.61	21.17	86.85
CarbNS <i>P. aeruginosa</i> (252)	75.38	76.08	38.73	98.35
CarbNS <i>A. baumannii</i> (361)	16.23	7.77	0.47	85.14
<i>S. maltophilia</i> (218)	42.88	34.27	34.52	78.17

Carbapenem-non-susceptible, (CarbNS) strains was defined as MEPM MIC ≥2 µg/mL for Enterobacteriaceae, ≥4 µg/mL for non-fermenters. *Burkholderia* spp. and *Serratia* spp. were not included as CST-resistant strains.  
CAZ/AVI = ceftazidime/avibactam; CEF/TAZ = ceftalozane/tazobactam; CPFX = ciprofloxacin; CST = colistin.

# Medical Need in cUTI: Conclusions

- **Urgent need for new antibiotics for CR cUTI**
  - >60% of CR pathogens in the urine are non-fermenters
  - WHO Critical Pathogens: CR *P. aeruginosa*, CR *A. baumannii*, and CREs
- **In cUTI CR pathogens associated with substantial increase in morbidity and mortality**
  - Increased length of hospital and ICU stays
  - Double the mortality compared with carbapenem-susceptible strains
- **Limited treatment options in cUTI**
  - Gaps in coverage
  - Toxicity of some current antibiotics
  - Resistance
- **Need new treatment options that address all 3 mechanisms of resistance**

# Microbiology and Clinical Pharmacology of Cefiderocol

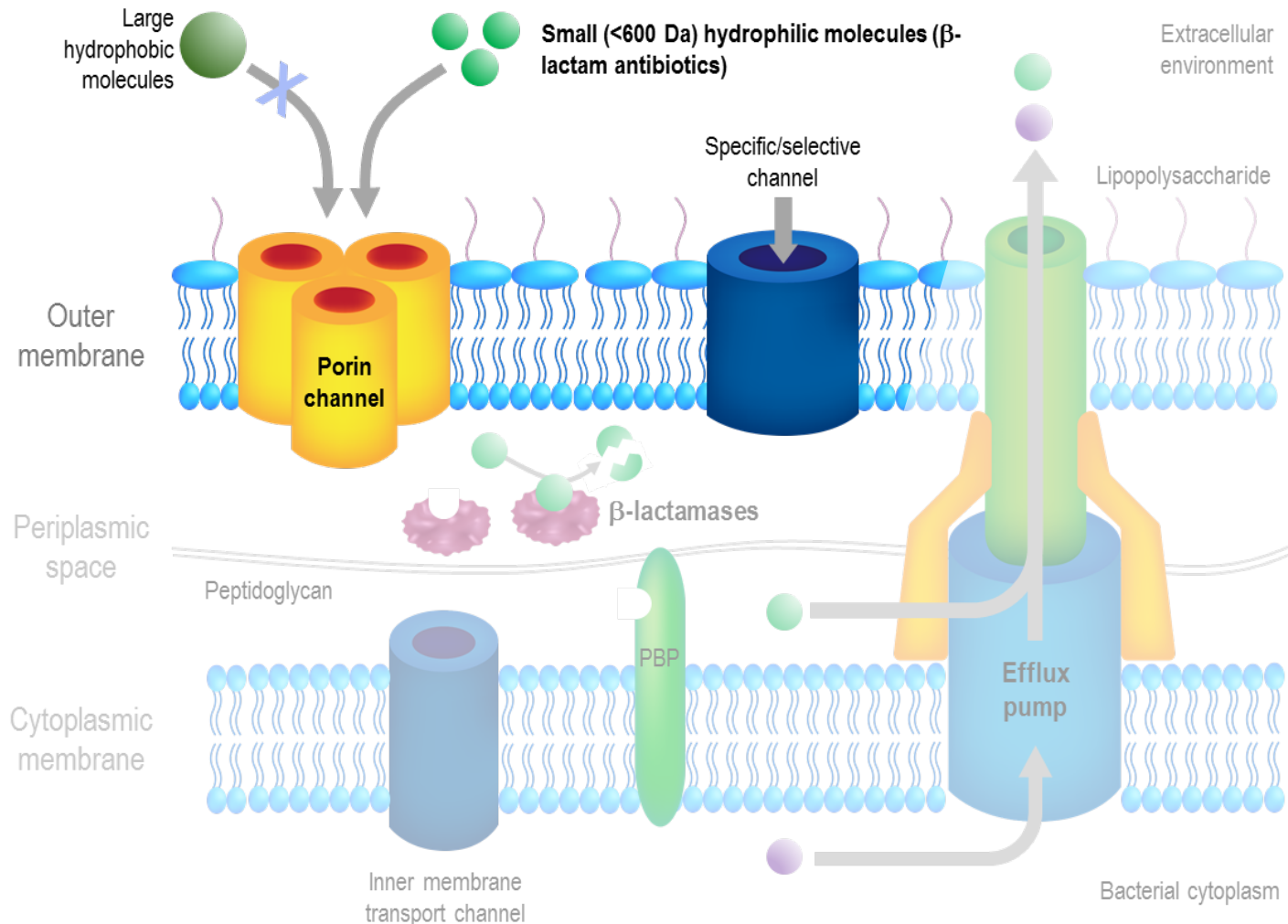
**Roger Echols, MD, FIDSA**

Clinical Development  
Shionogi Inc.

# Cefiderocol

- **Siderophore cephalosporin**
  - Unique method of cell entry
- **Stable to all classes of beta-lactamases**
  - Serine (KPC, OXA) and metallo-carbapenemases (NDM, VIM, IMP)
- **Overcomes all 3 beta-lactam resistance mechanisms**
  - Porin channel mutations
  - Efflux pump overproduction
  - Beta-lactamase stability

# The Outer Membrane Barrier of Gram-negative Bacteria<sup>1,2</sup>



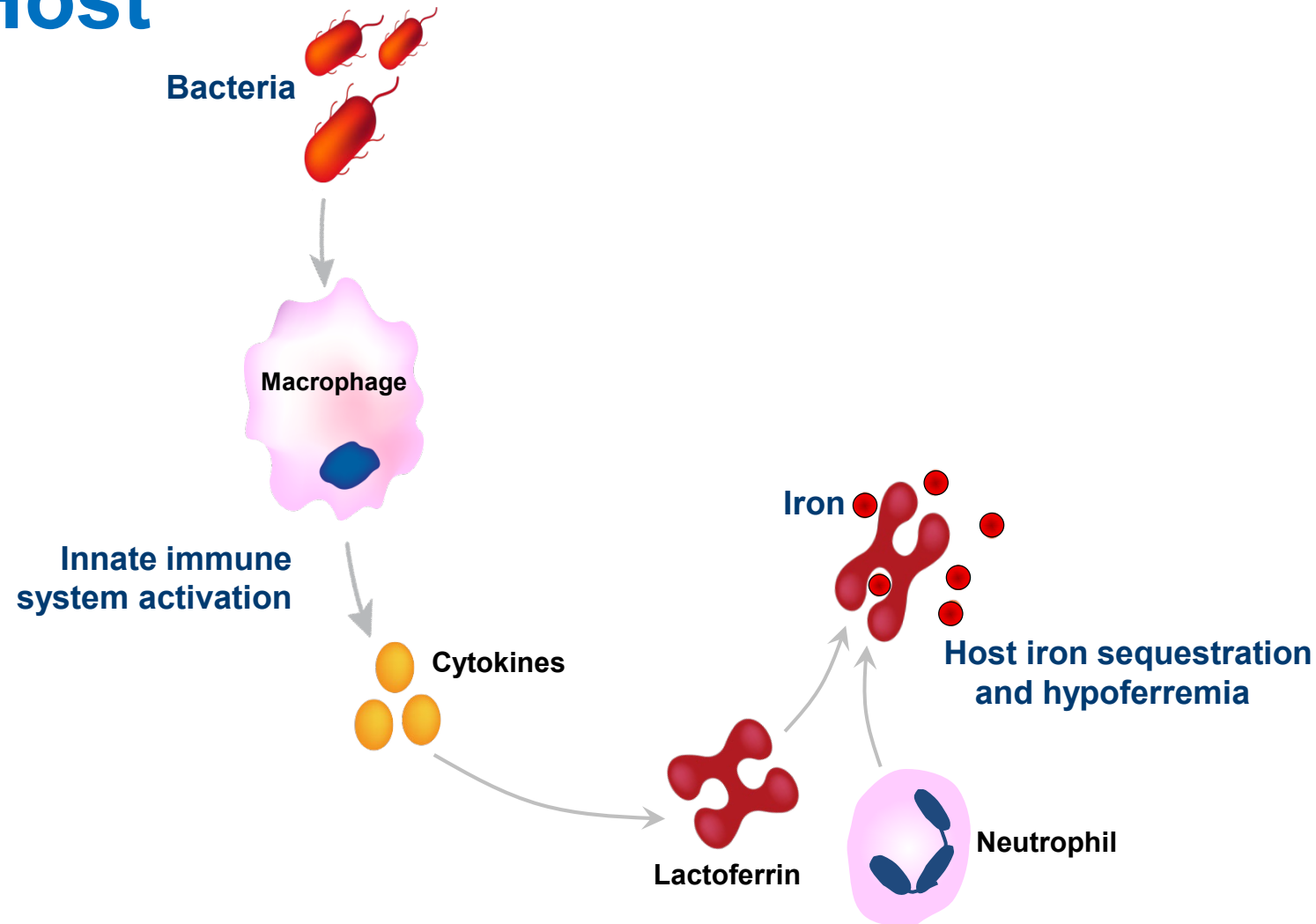
PBP = penicillin binding protein.

1. Zgurskaya HI, et al. *ACS Infect Dis.* 2015;1(11):512-522.

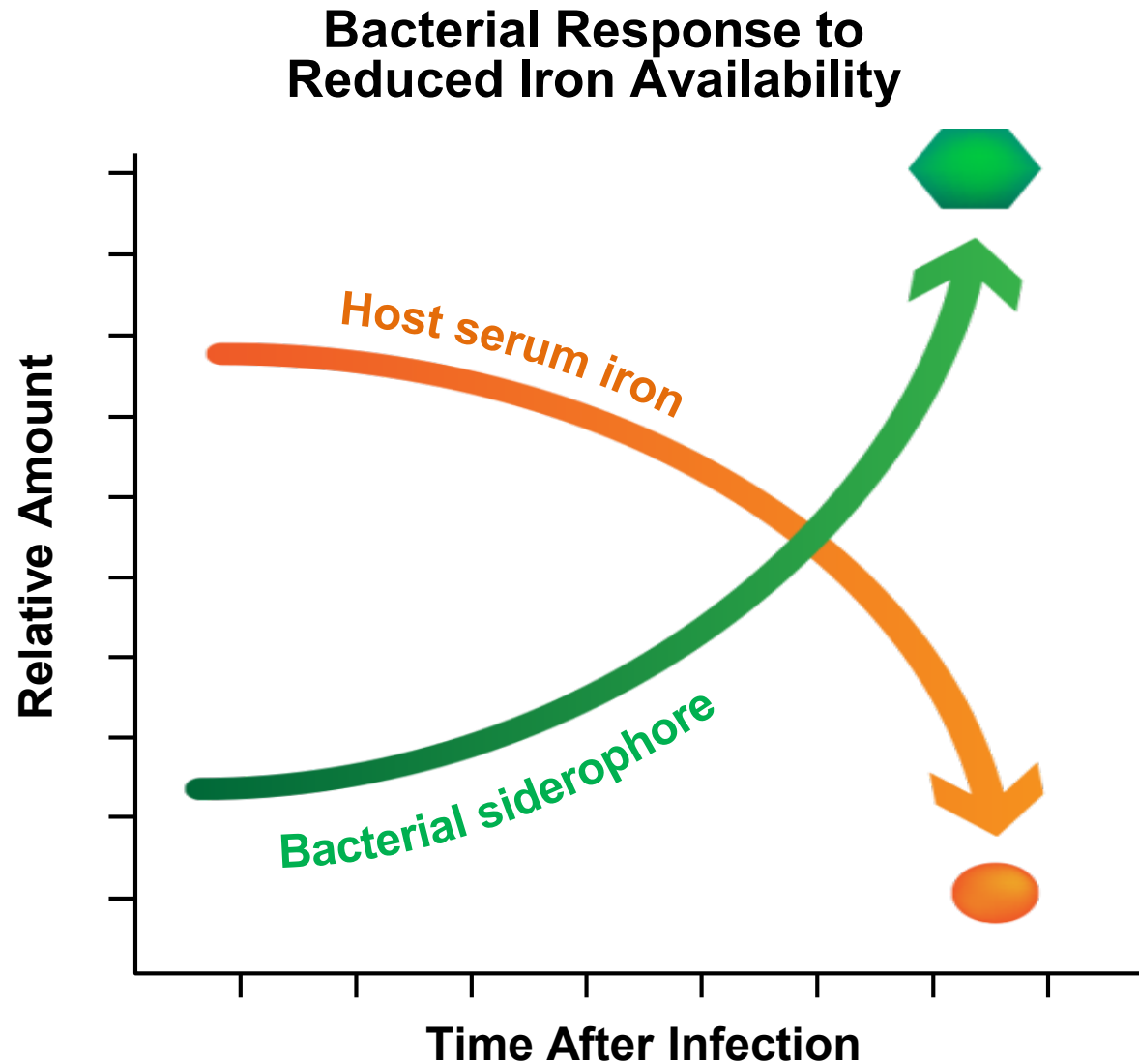
2. Blair JM, et al. *Nat Rev Microbiol.* 2015;13(1):42-51.

# Battle for Iron: Host vs Pathogen

## Host

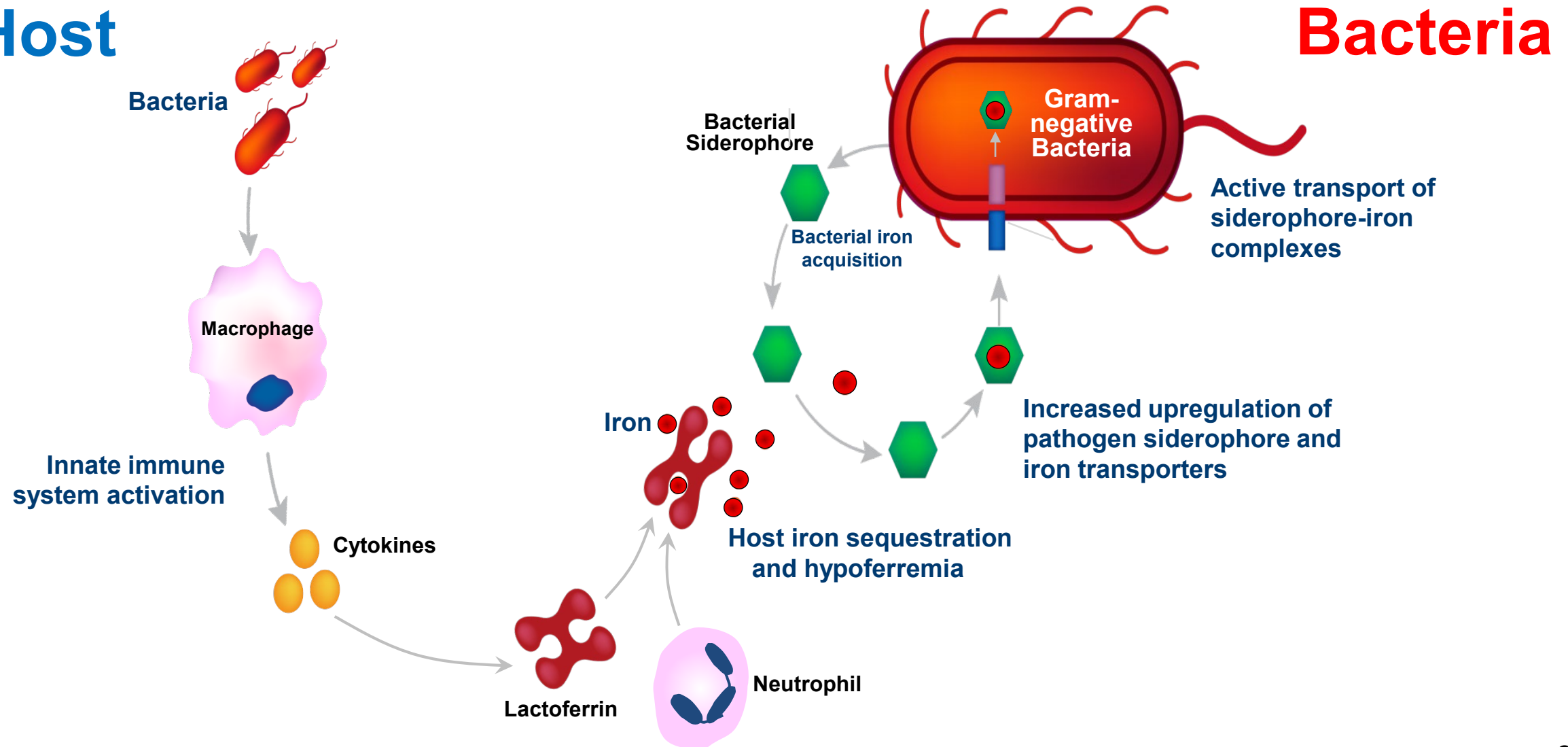


# Battle for Iron: Host vs Pathogen



# Battle for Iron: Host vs Pathogen

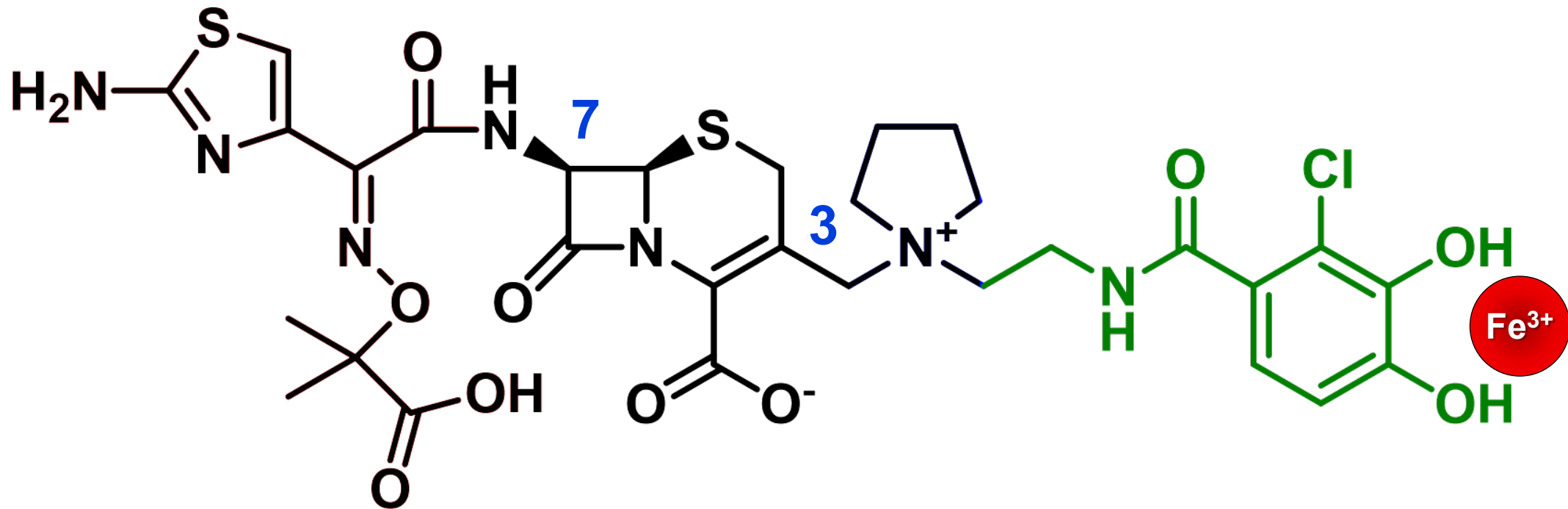
## Host



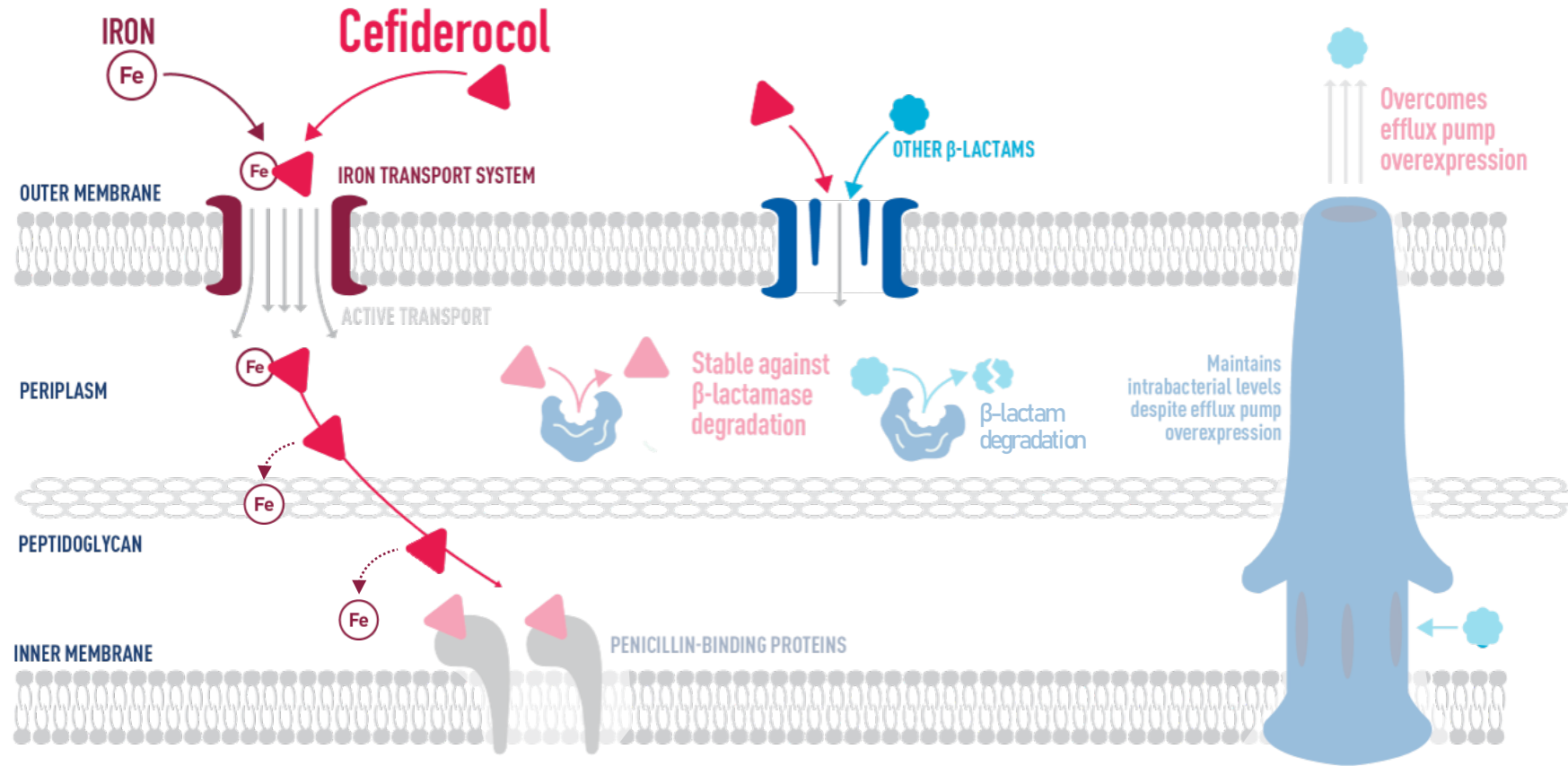
# Cefiderocol: Siderophore Cephalosporin

Cephalosporin

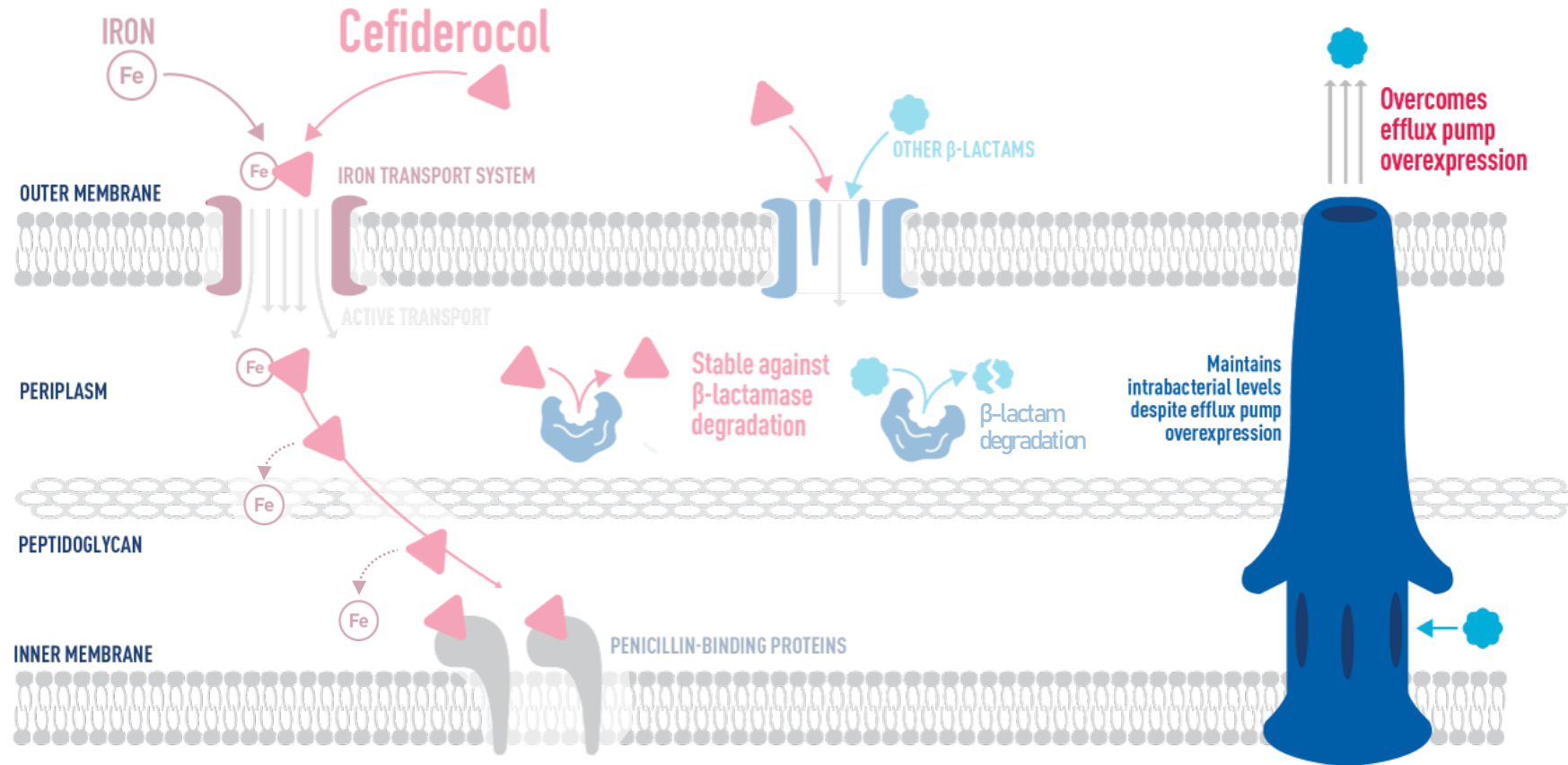
Catechol Moiety



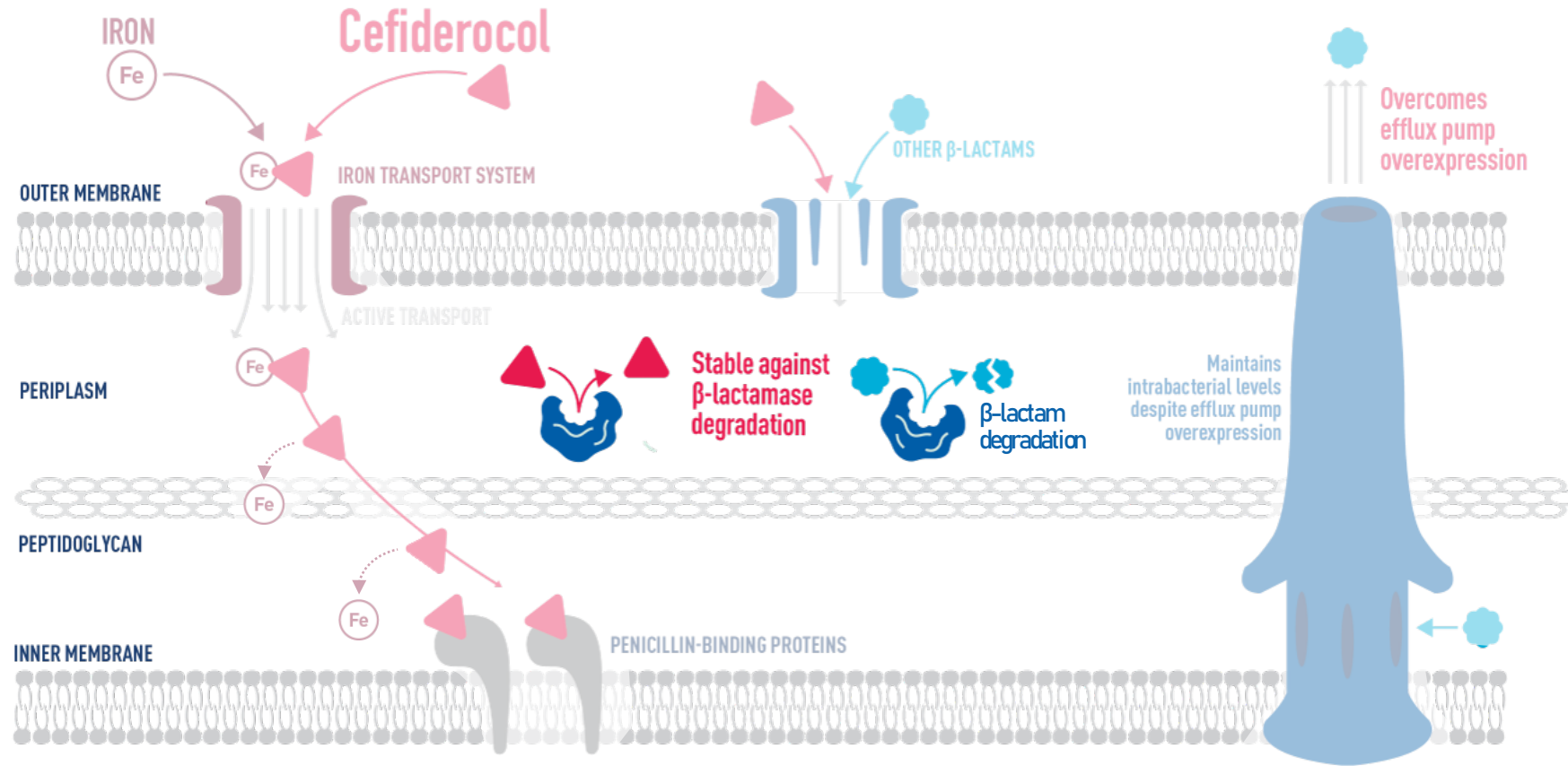
# Cefiderocol Overcomes the Three Mechanisms of Resistance



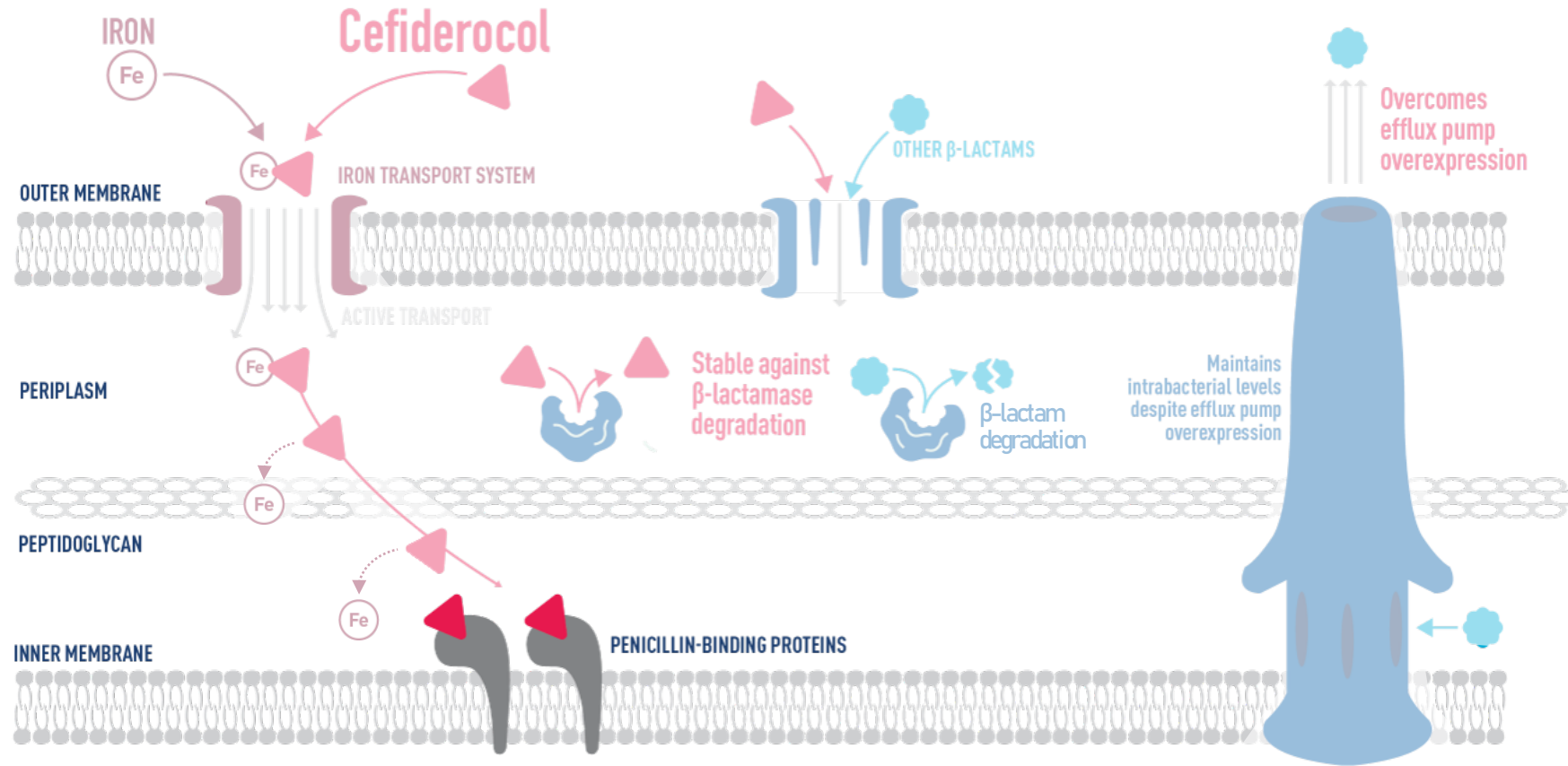
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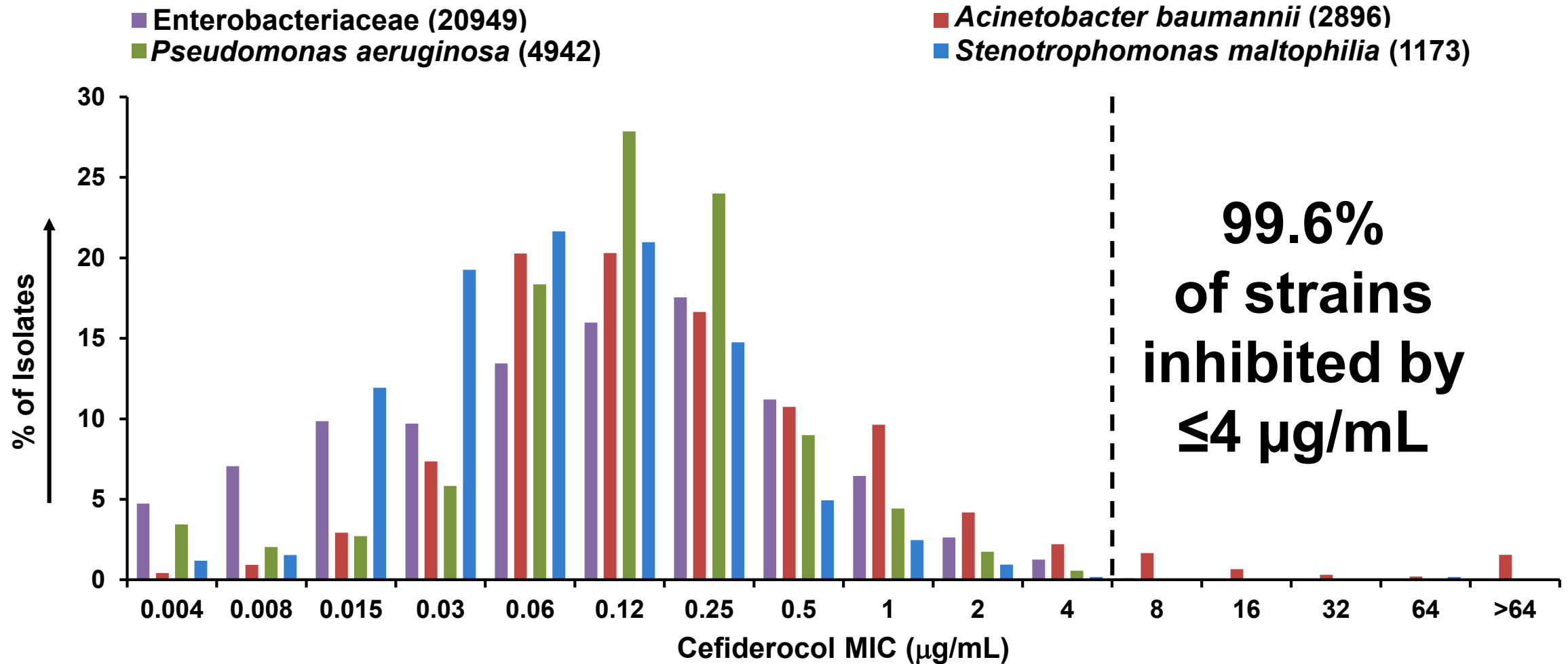


# Cefiderocol Stability Against Beta-lactamases

Molecular Class	Type	Example Enzymes (Carbapenemases)	Cefiderocol
A	Serine	KPC, TEM, SHV, CTX-M	Stable
C	Serine	AmpC, CMY	Stable
D	Serine	OXA-48, OXA 23/24	Stable
B	Metallo	IMP, VIM, NDM	Stable

# Cefiderocol Activity Against Clinical Isolates

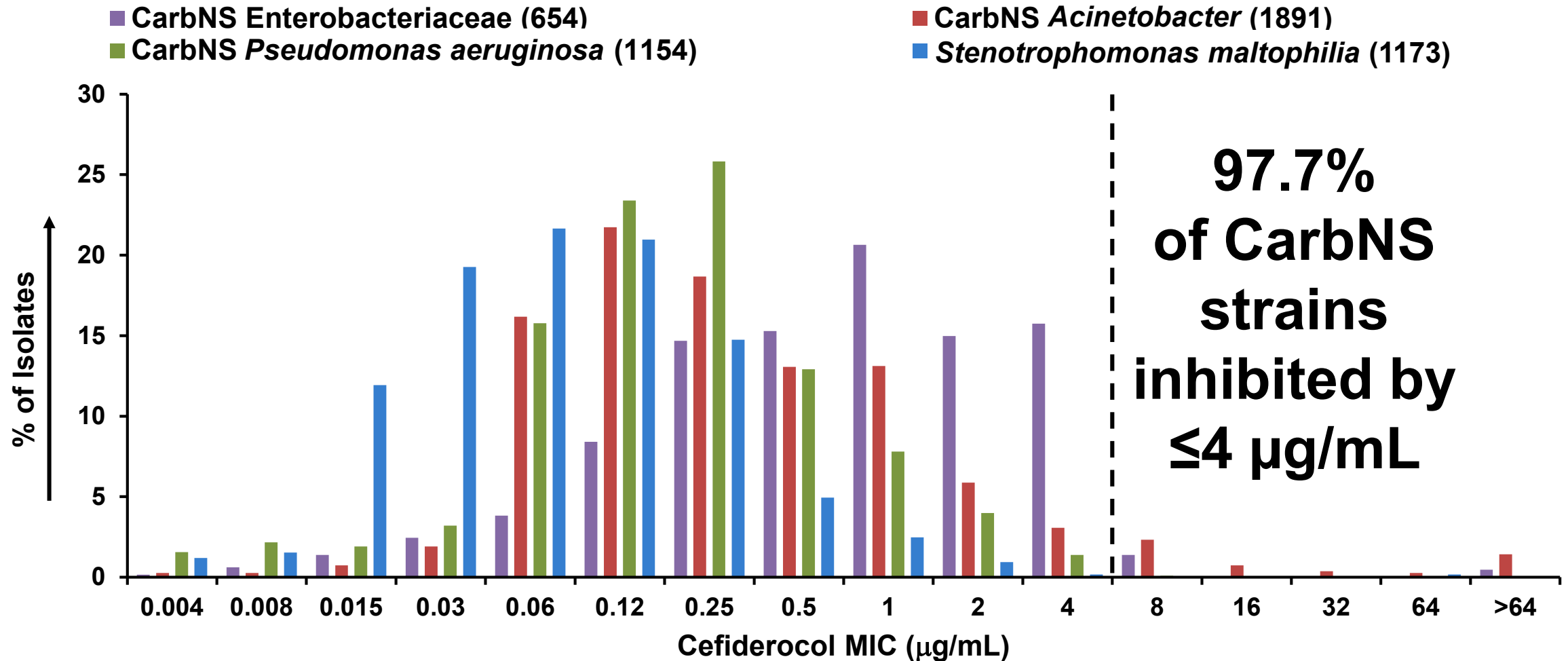
## SIDERO-WT-2014-2016



MIC distribution of 29,960 Gram-negative clinical isolates from multi-national SIDERO-WT-2014-2016

# Cefiderocol Activity Against Carbapenem Non-Susceptible Clinical Isolates

## SIDERO-WT-2014-2016



MIC distribution of 4862 CarbNS Gram-negative clinical isolates from multi-national SIDERO-WT-2014-2016

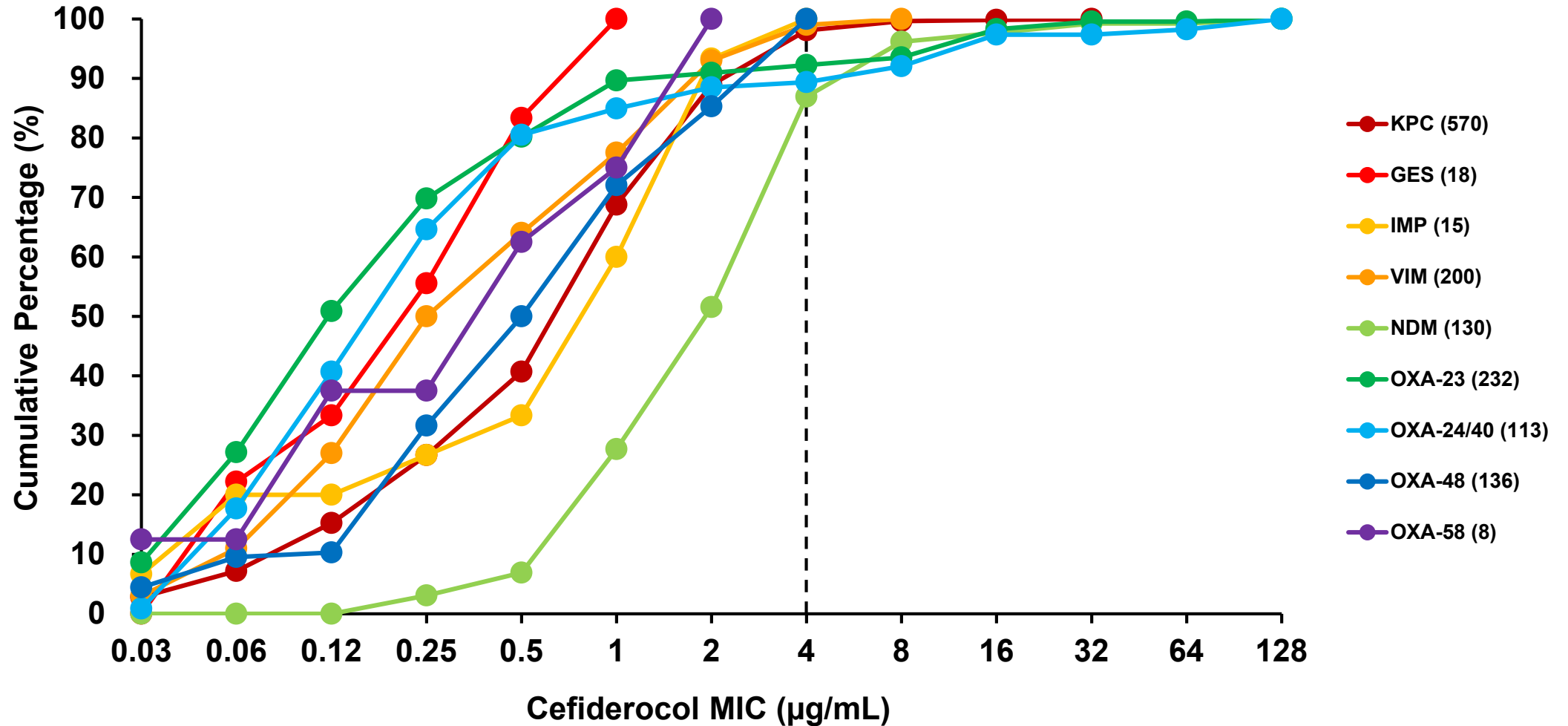
# Susceptibility of Carbapenem Non-Susceptible Clinical Isolates

## SIDERO-WT-2014-2016

Species (Number of Strains)	Susceptibility Percentage (%)				
	Cefiderocol (MIC ≤4)	CAZ/AVI (MIC ≤8)	CEF/TAZ (MIC ≤2 or 4)	Ciprofloxacin (MIC ≤1)	Colistin (MIC ≤2)
All Gram-negatives (30459)	99.45	90.20	84.28	72.93	95.49
CarbNS Enterobacteriaceae (654)	98.16	77.67	8.40	13.91	75.55
CarbNS non-fermenters (4331)	97.57	40.96	34.61	21.17	86.85
CarbNS <i>P. aeruginosa</i> (1154)	99.91	75.38	76.08	38.73	98.35
CarbNS <i>A. baumannii</i> (1891)	94.87	16.23	7.77	0.47	85.14
<i>S. maltophilia</i> (1173)	99.82	42.88	34.27	34.52	78.17

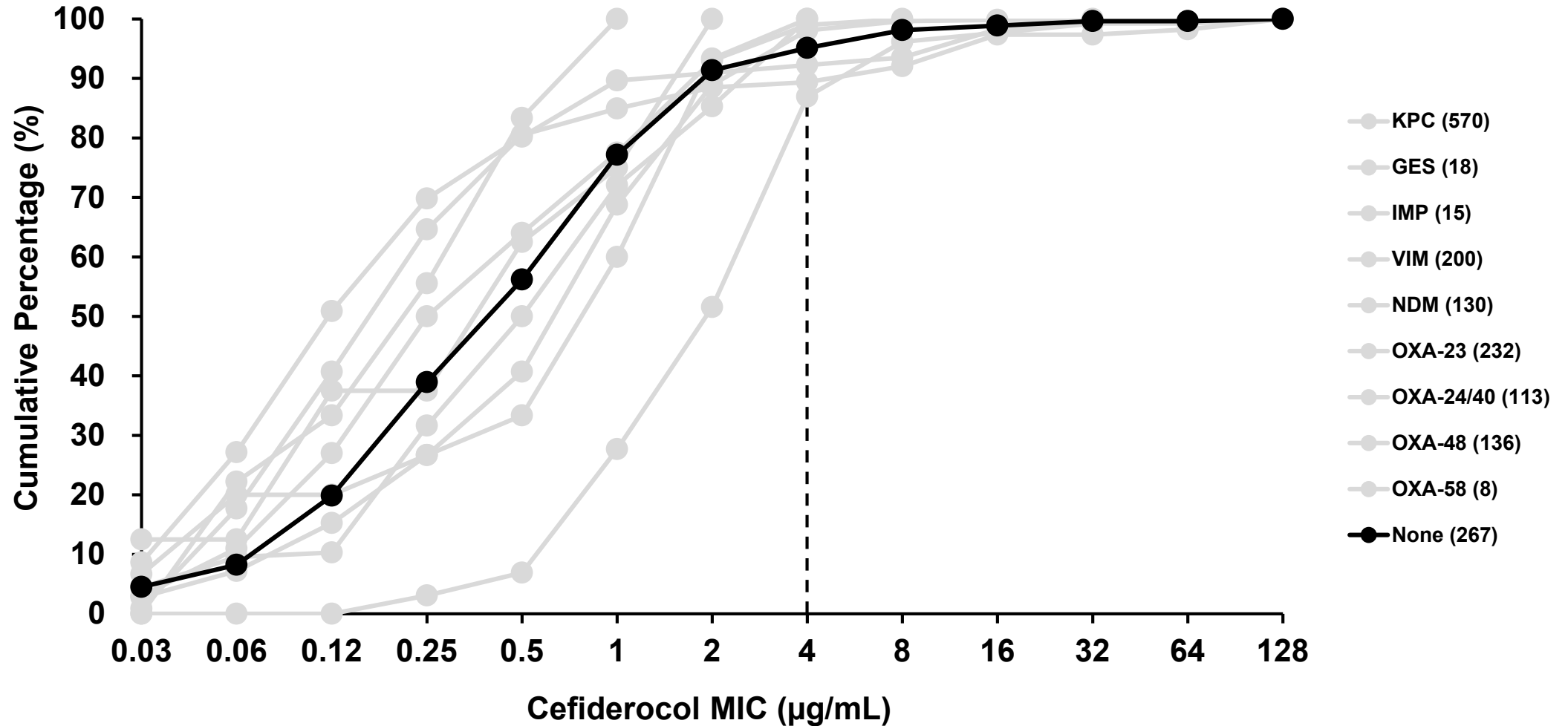
# Cefiderocol Activity Against Carbapenemases

## SIDERO-CR Study



# Cefiderocol Activity Against Carbapenemases

## SIDERO-CR Study



# Development of Resistance to Cefiderocol

- **Cefiderocol has low propensity of developing resistance as assessed by**
  - Serial passage for selection of resistant mutants
  - Frequency of resistance with large inocula
  - Resistance acquisition under dynamic human drug exposure (chemostat)
  - Impact of loss of iron transport channels
  - Adaptive resistance (discordance of in vitro activity and in vivo efficacy)
  - Emergence of resistance on therapy

# Gram-negative Only Activity

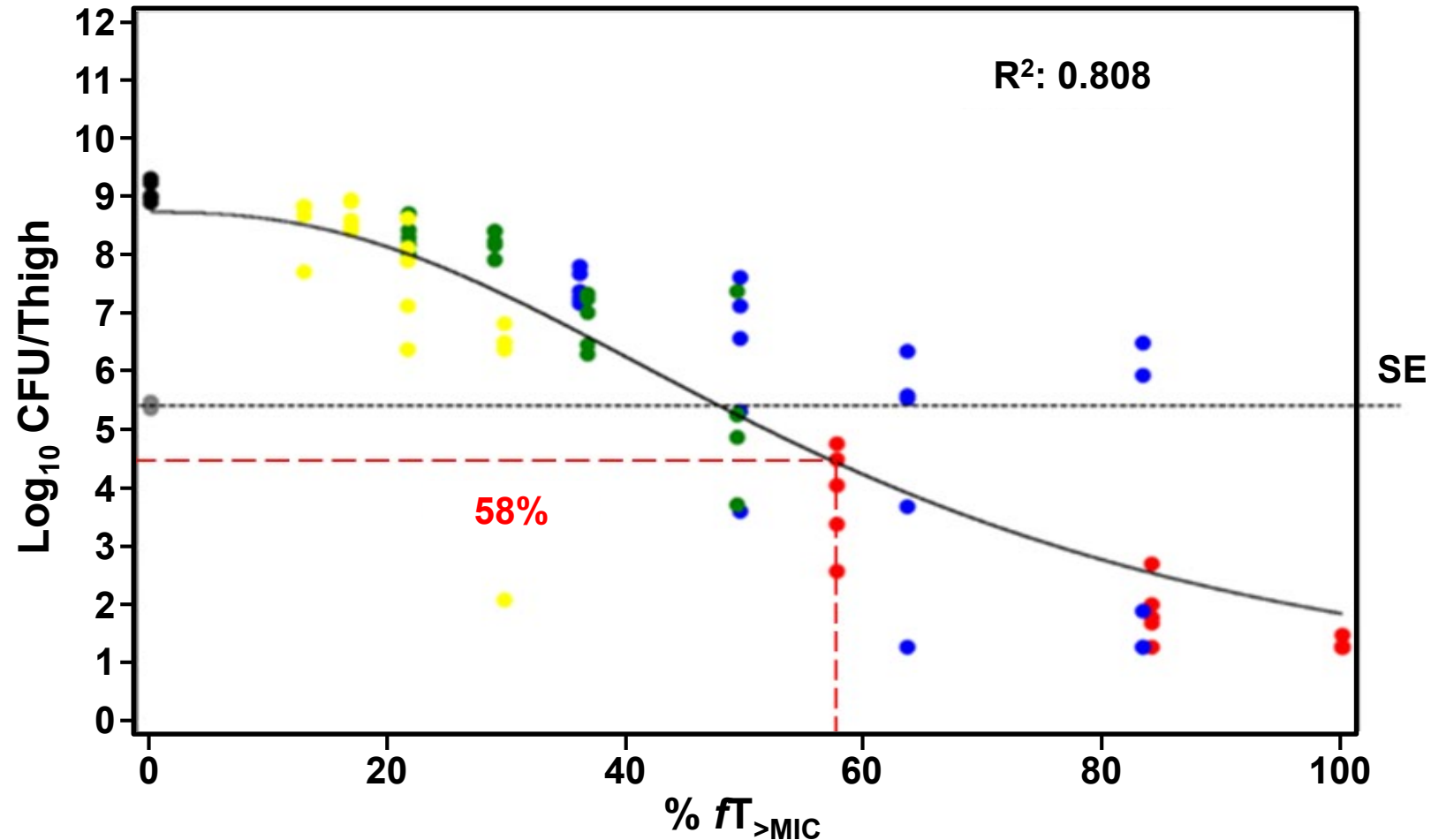
- **Cefiderocol has no relevant activity against aerobic Gram-positive or anaerobic bacteria**
  - Narrow spectrum antibiotic
- **Additional antibiotics may be needed for Gram-positive or anaerobic activity**

# Human Dose Selection

- **Selection of a dose and dosing regimen for antibiotics often based on empirical evidence from phase 1 and 2 clinical trials**
- **Rigorous PK/PD analyses often performed after drug is marketed**
- **Cefiderocol being developed under a streamlined program with limited clinical trial data**
- **Cefiderocol development includes patients with life-threatening infections**

# Pharmacodynamic (PD) Target: Dose Fractionation

● Not Treated (0hr)   ● Not Treated (24hr)   ● q3h   ● q6h   ● q12h   ● q24h

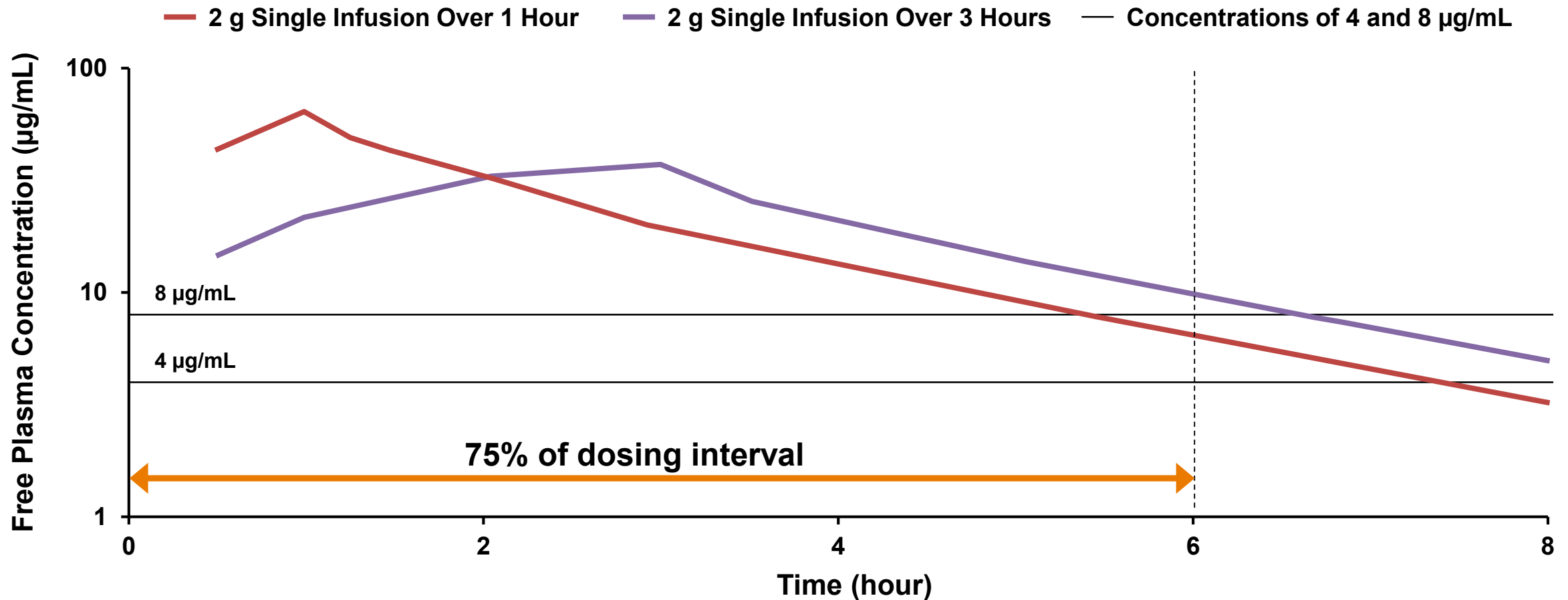


# Dose Response Studies

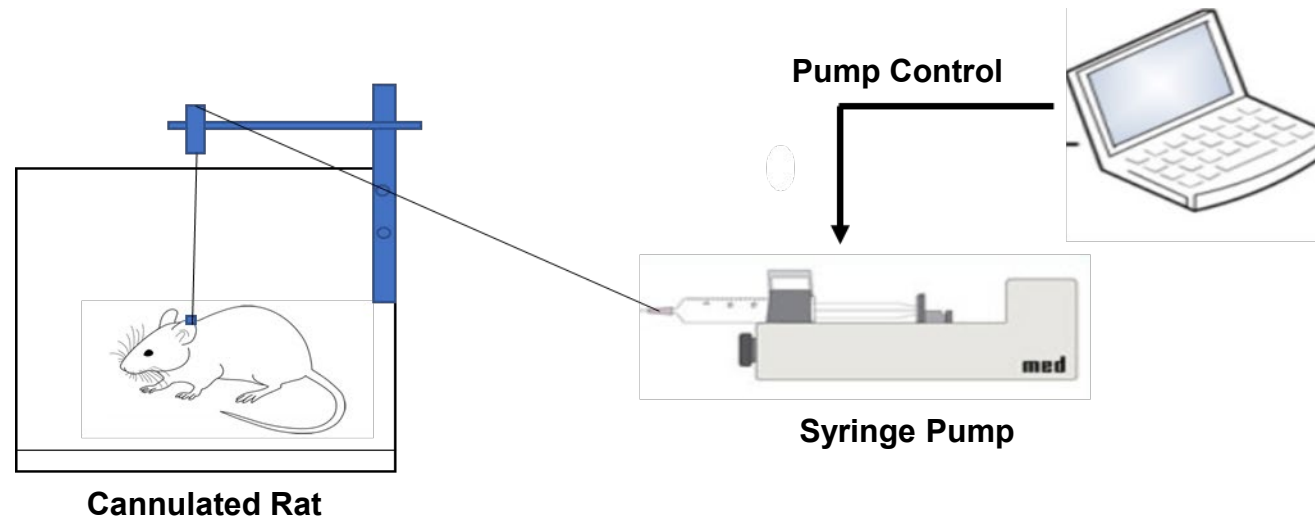
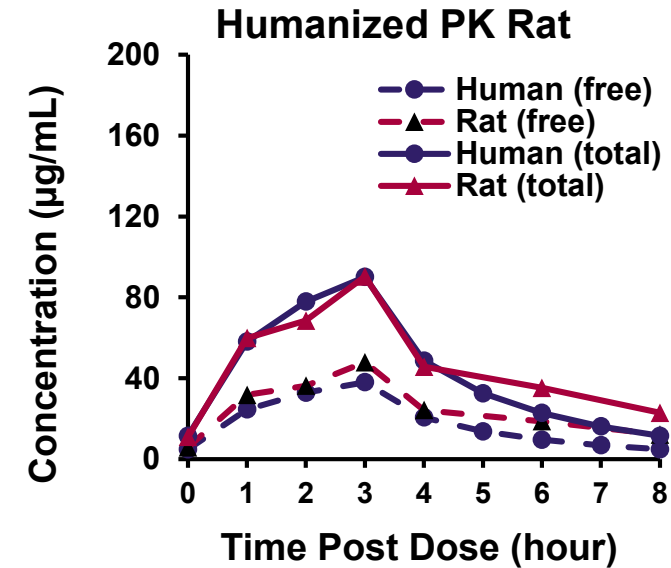
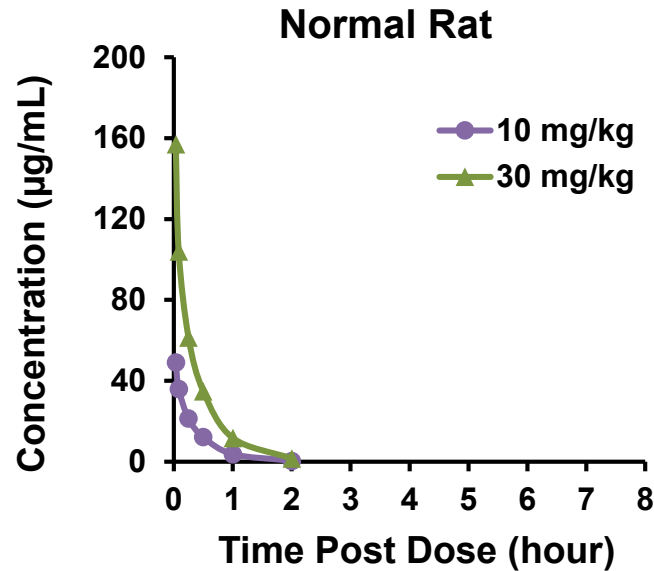
- **Multiple dose response studies**
  - CS and CR (NDM, VIM, KPC, IMP)
  - Enterobacteriaceae and non-fermenters
  - Lung and thigh
- **%fT>MIC variable, range 30-100%**
  - Same for lung and thigh
  - Average for thigh = 75%

# Human Pharmacokinetics (Healthy Subjects)

## Free Plasma Concentration Profiles with 1-hr and 3-hr Infusions

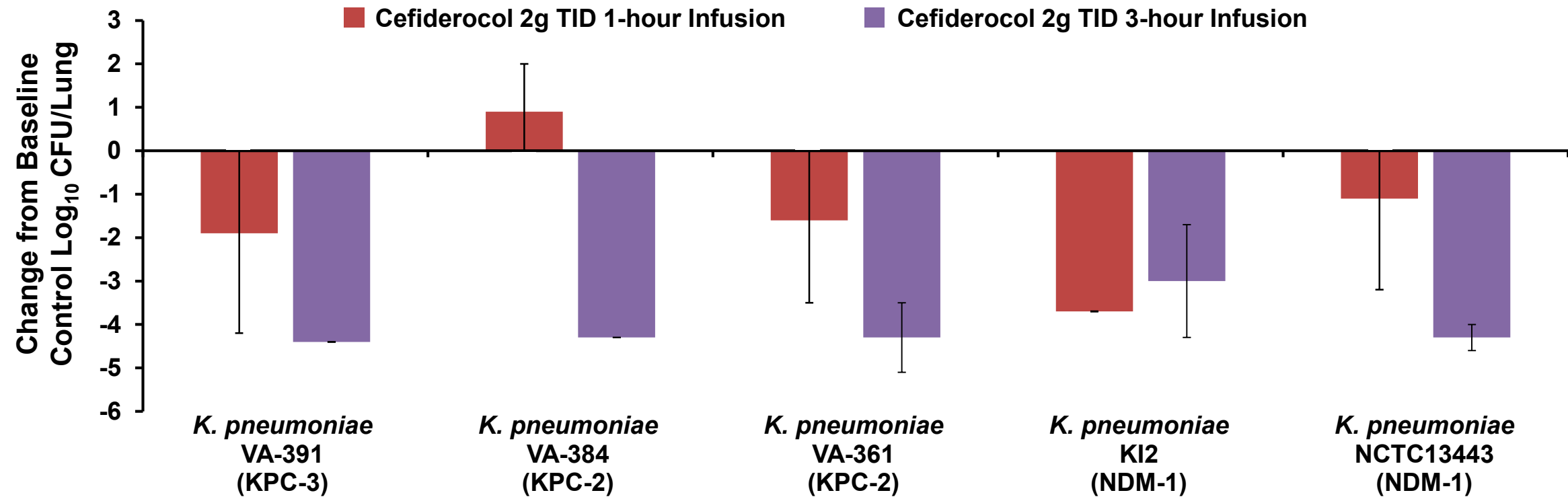


# Efficacy in Rat Pneumonia Model with Human PK Exposure



# Cefiderocol Efficacy: 1- vs 3-Hour Infusion

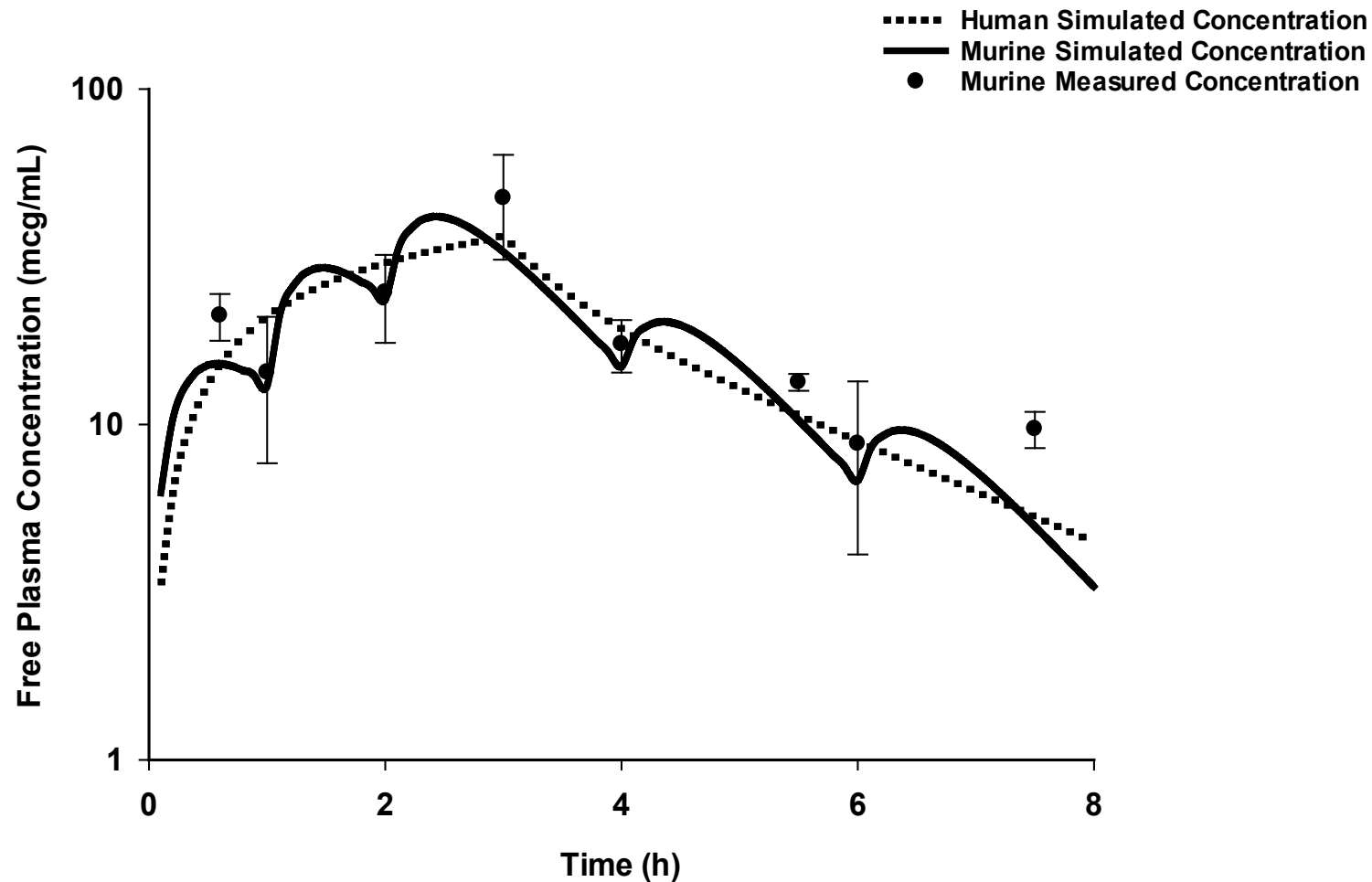
## Rat Lung Infection Model



MIC				
Cefiderocol	4	4	4	8
Ceftadizime	>32	>32	>32	>32
Meropenem	16	>32	16	>32

# Mouse Infection Model Under Human PK of 2 Grams Infused Over 3 hours

## Humanized PK by Frequent Dosing Using Renal Impaired Mouse

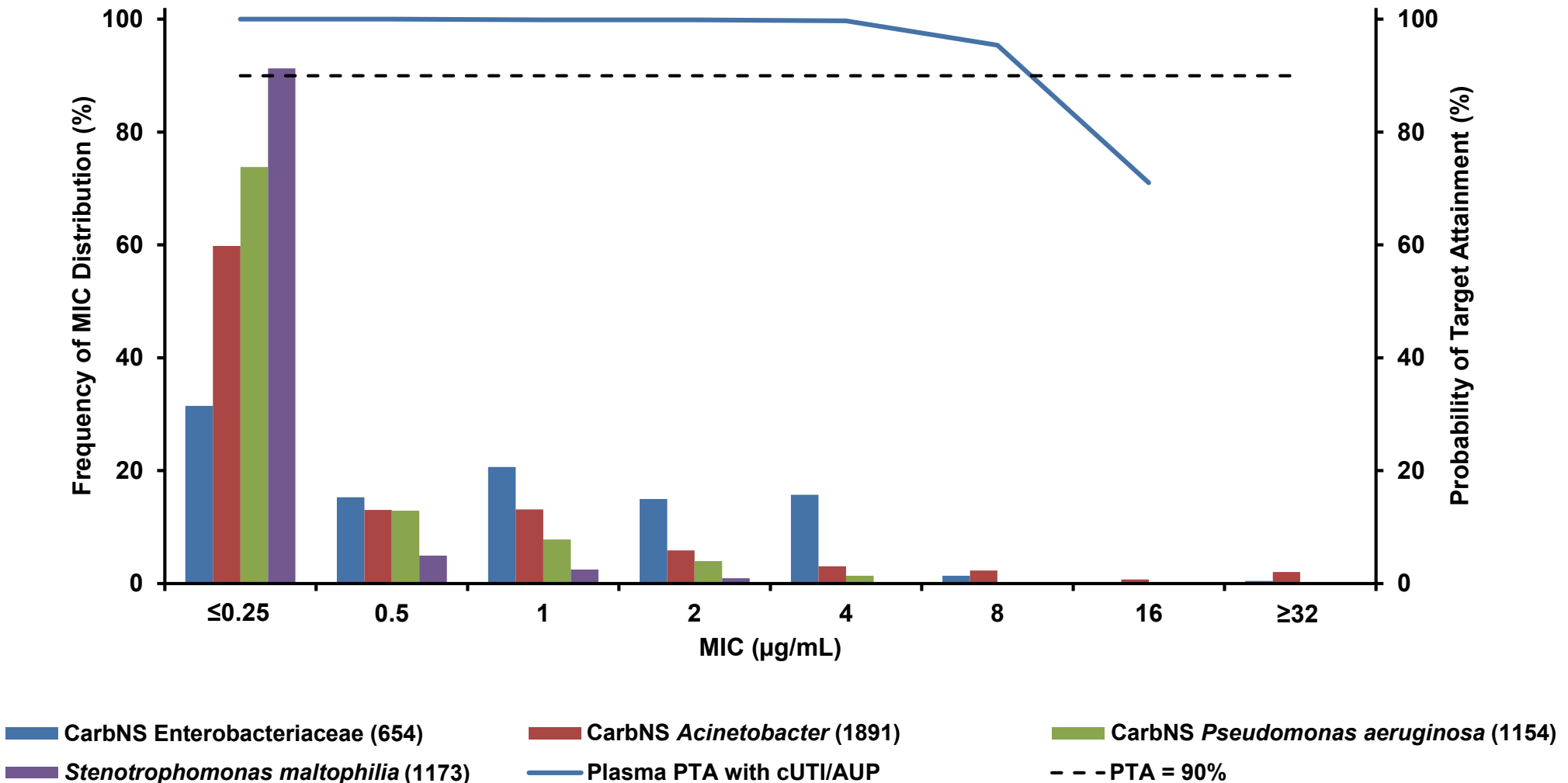


# Efficacy Using Mouse Thigh Infection Model Under Human PK

	Number of Strains Against Which Cefiderocol Was Effective/Total Number of Strains							
	0.12	0.25	0.5	1	2	4	8	≥16
Enterobacteriaceae	1/1	2/2	4/4	5/5	5/5	12/14	2/2	1/6
<i>P. aeruginosa</i>	0/0	2/2	5/5	7/7	1/2	4/4	0/1	0/0
<i>A. baumannii</i>	3/3	2/2	4/4	3/3	3/3	1/1	1/3	4/16
Total	4/4	6/6	13/13	15/15	9/10	17/19	3/6	5/22

64/67 (96%)  
Enterobacteriaceae 94%  
*P. aeruginosa* 95%  
*A. baumannii* 100%

# PTA for 75% fT>MIC in CREDIBLE cUTI Patients for 2 Grams q8h Over 3 Hours



# Clinical Pharmacology Profile of Cefiderocol

- **Linear PK in the range of tested dose (0.1 to 4g)**
- **Elimination half-life of 2 to 3 hours (no accumulation with 2g q8h)**
- **90% excreted via the kidney as unchanged cefiderocol**
- **Dose adjustment based on renal function**
- **60% protein binding**
- **No drug interactions via CYP enzymes and drug transporters**
- **No QT prolongation at supratherapeutic dose of 4g**
- **Well tolerated at 2g q8h**
- **Safety profile similar to other cephalosporins**

# Microbiology and Clinical Pharmacology

## Conclusions

- **Cefiderocol overcomes all three mechanisms of carbapenem resistance**
  - Siderophore cell entry
  - Broad beta-lactamase stability
- **Consistent efficacy demonstrated in animal infections using human drug exposures**
- **Low propensity for development of resistance**
- **PK/PD and PTA estimates confirmed by human data in patients**
  - Dosing adjusted for renal function, including Augmented Renal Clearance (ARC)

# cUTI Efficacy and Safety

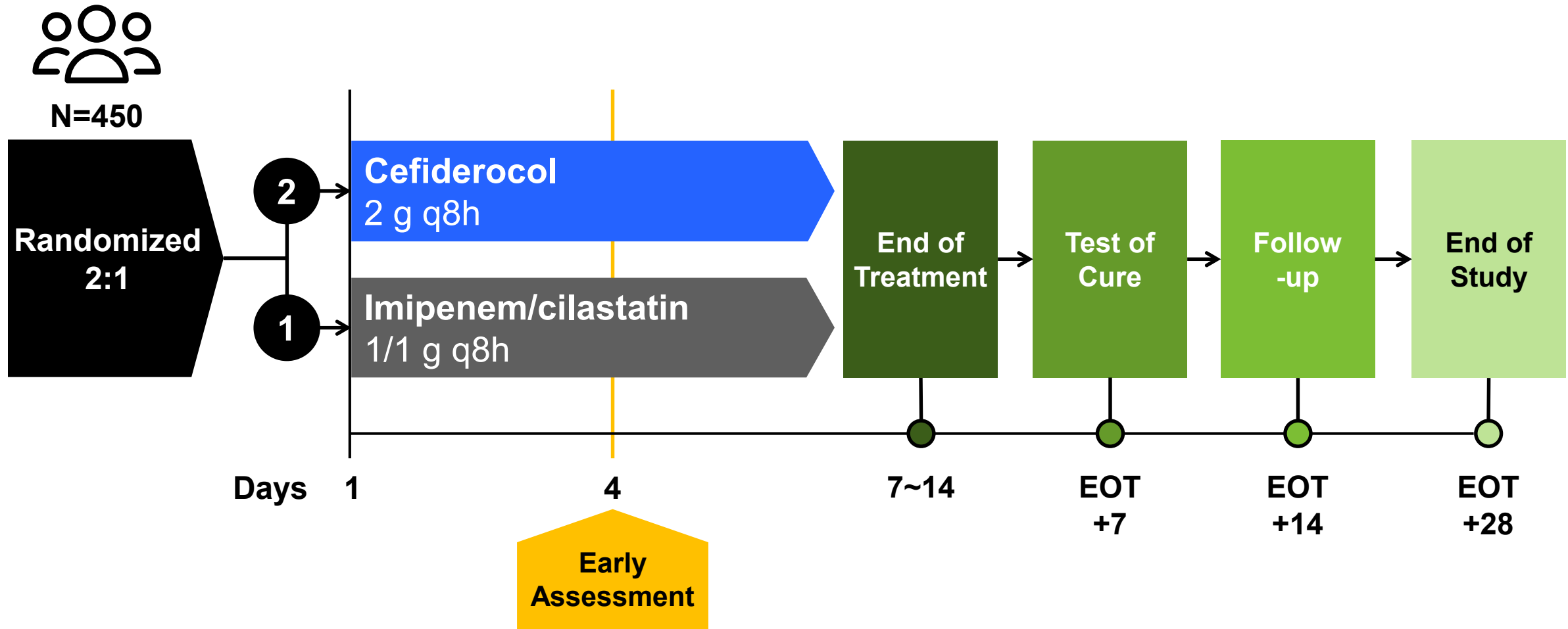
**Simon Portsmouth, MBChB, MD, FRCP**

Executive Medical Director, Medical Science  
Shionogi Inc.

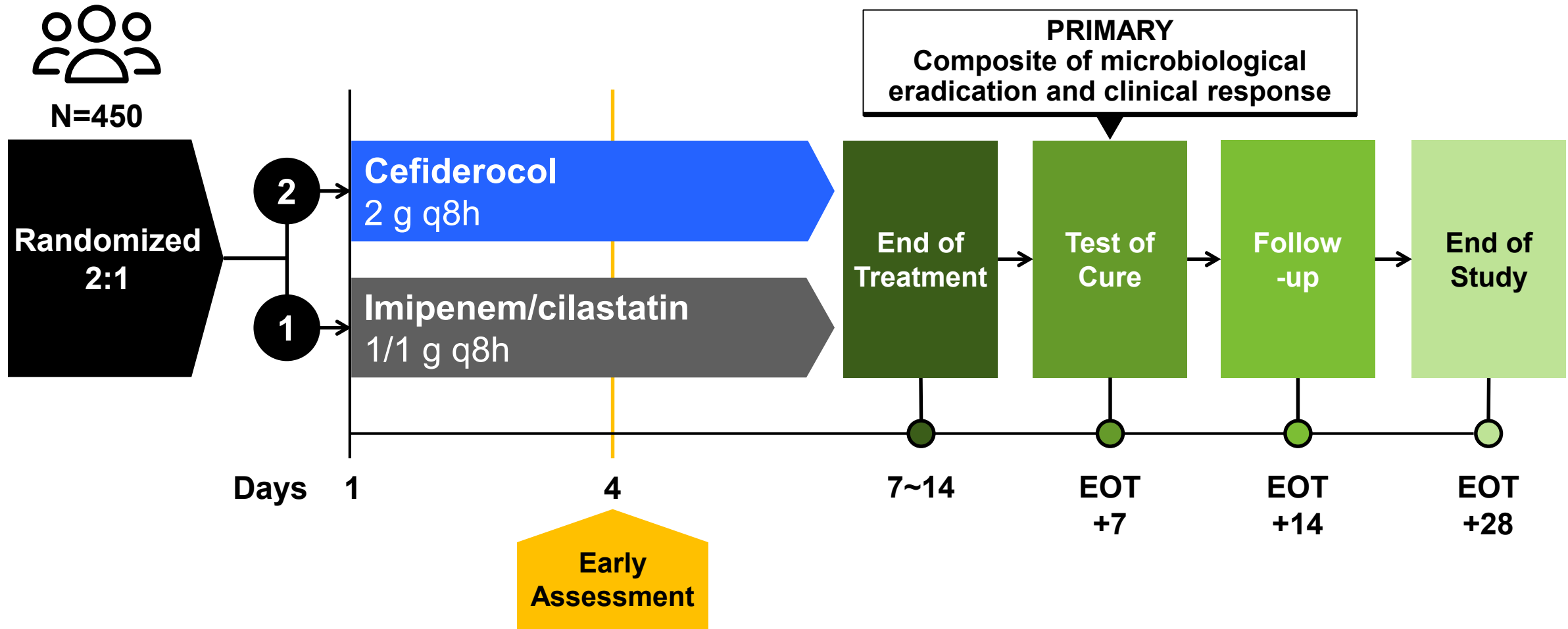
# Pivotal Cefiderocol cUTI Study

- **Double-blind, randomized, non-inferiority study**
- **450 hospitalized patients**
  - 300 treated with cefiderocol
  - 150 treated with imipenem/cilastatin 1g/1g

# cUTI Study Design



# cUTI Study Design

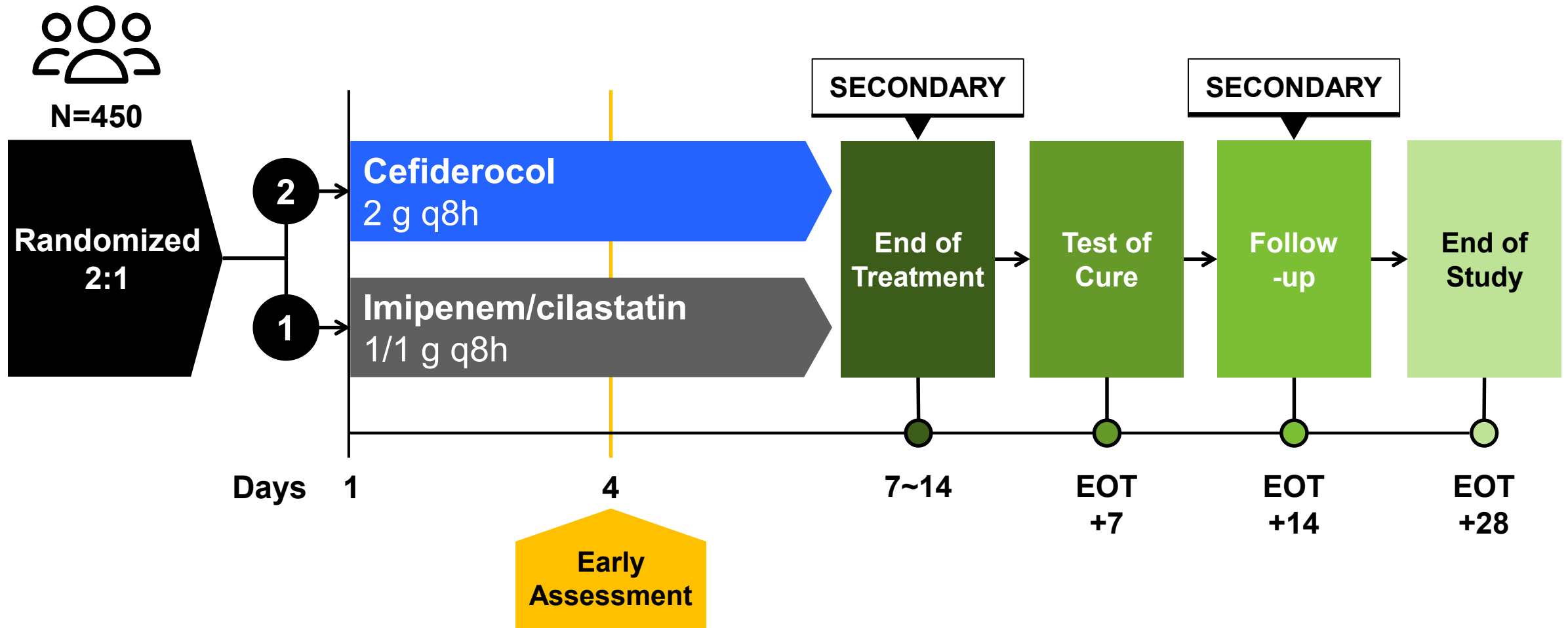


# Study Populations

## cUTI Study

- **Micro-ITT: Microbiological Intent-To-Treat**
  - Qualifying Gram-negative pathogen and at least one dose of study drug
- **ME: Microbiologically Evaluable**
  - Qualifying Gram-negative pathogen and adherence to aspects of protocol such as treatment duration

# cUTI Study Design



# Unique Study Features

## cUTI Study

- **Population at risk of multiple drug resistant infections**
- **No more than 30% with acute uncomplicated pyelonephritis**
- **Few exclusion criteria**

# Baseline Characteristics: Population at Risk for MDR Infection cUTI Study

Micro-ITT Population	Cefiderocol N=252 %	Imipenem/Cilastatin N=119 %
Gender (female)	52.8	59.7
Age (years, mean)	62.3	61.3
≥65 years of age	55.2	54.6
≥75 years of age	24.2	24.4
Race (White)	95.6	96.6
Clinical Diagnosis at Baseline		
cUTI w/ or w/o pyelonephritis	74.2	70.6
Pyelonephritis	51.6	53.8
Acute uncomplicated pyelonephritis	25.8	29.4
History of stones	25	32
Urinary catheter	18	14
Obstructive uropathy	34	32
Blood stream infection	7	7

# Baseline Characteristics: Population at Risk for MDR Infection

## cUTI Study

Micro-ITT Population	Cefiderocol N=252 %	Imipenem/Cilastatin N=119 %
Creatinine clearance renal grading		
>50-80 mL/min (mild)	31.0	34.5
>30-50 mL/min (moderate)	16.3	19.3
<30 mL/min (severe)	2.8	3.4
Total	50.1	57.2

# Pathogens and Resistance at Baseline

## cUTI Study

Total Micro-ITT Population (N=371)	Cefiderocol N=252		Imipenem/Cilastatin N=119	
	%	Resistance	%	Resistance
<i>E. coli</i>	60.3	38% levofloxacin R 17% cefepime R	66.4	37% levofloxacin R 16% cefepime R
<i>K. pneumoniae</i>	19.0	53% levofloxacin R 53% cefepime R	21.0	56% levofloxacin R 56% cefepime R
<i>P. aeruginosa</i>	7.1		4.1	
<i>P. mirabilis</i>	6.7		1.7	
<i>E. cloacae</i> complex	3.6		0.8	

# Baseline Imipenem Resistance

cUTI Study

Total Micro-ITT Population N=371	Cefiderocol N=252		Imipenem/Cilastatin N=119	
	%	IPM Resistance <sup>1</sup> n/N	%	IPM Resistance <sup>1</sup> n/N
<i>E. coli</i>	60.3	0/143	66.4	0/76
<i>K. pneumoniae</i>	19.0	5/45	21.0	1/23
<i>P. aeruginosa</i>	7.1	3/15	4.1	1/4
<i>P. mirabilis</i>	6.7	1/16	1.7	0/2
<i>A. calcoaceticus- baumannii</i> complex	0.0	0/0	0.8	1/1

1. CLSI breakpoint.

# Disposition

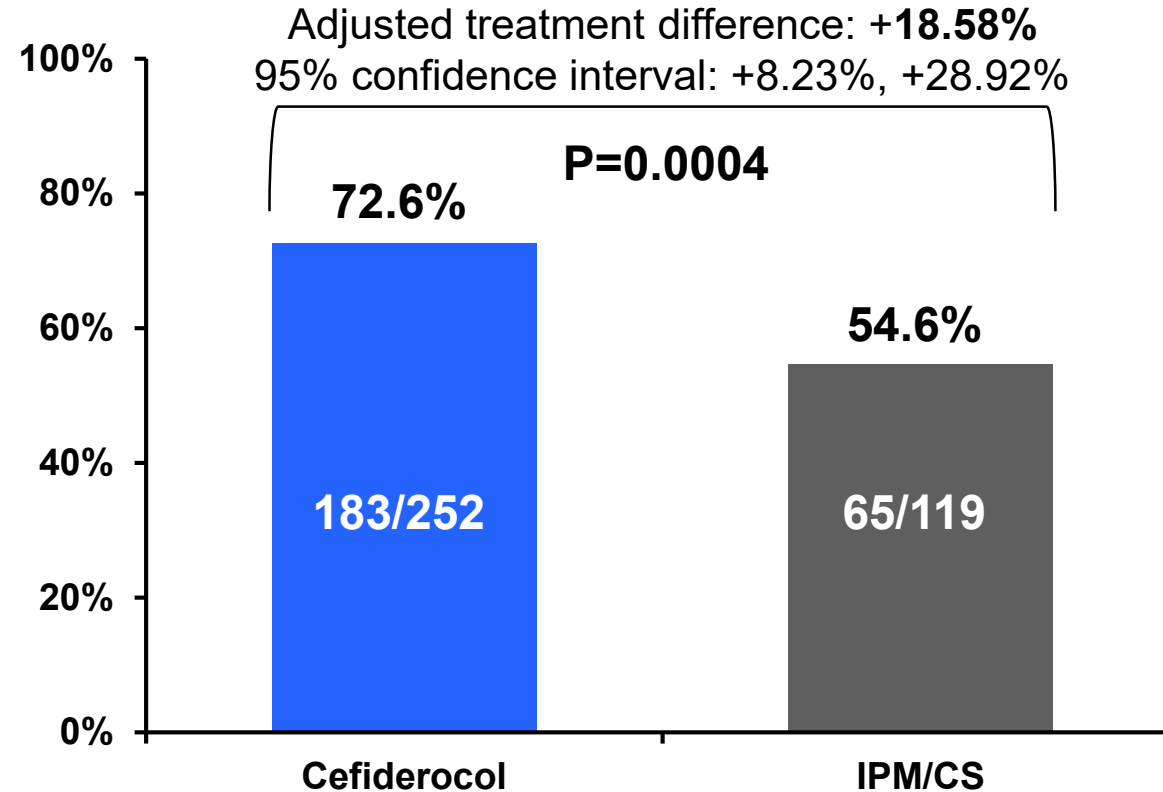
## cUTI Study

- **93% completed treatment in both groups**
- **Median duration of treatment was 9 days for both groups**
- **2 patients in each group interrupted treatment**
- **17% required dose adjustment post baseline**
- **Discontinuation due to AE in 5 cefiderocol and 3 imipenem treated patients**

# Primary Endpoint

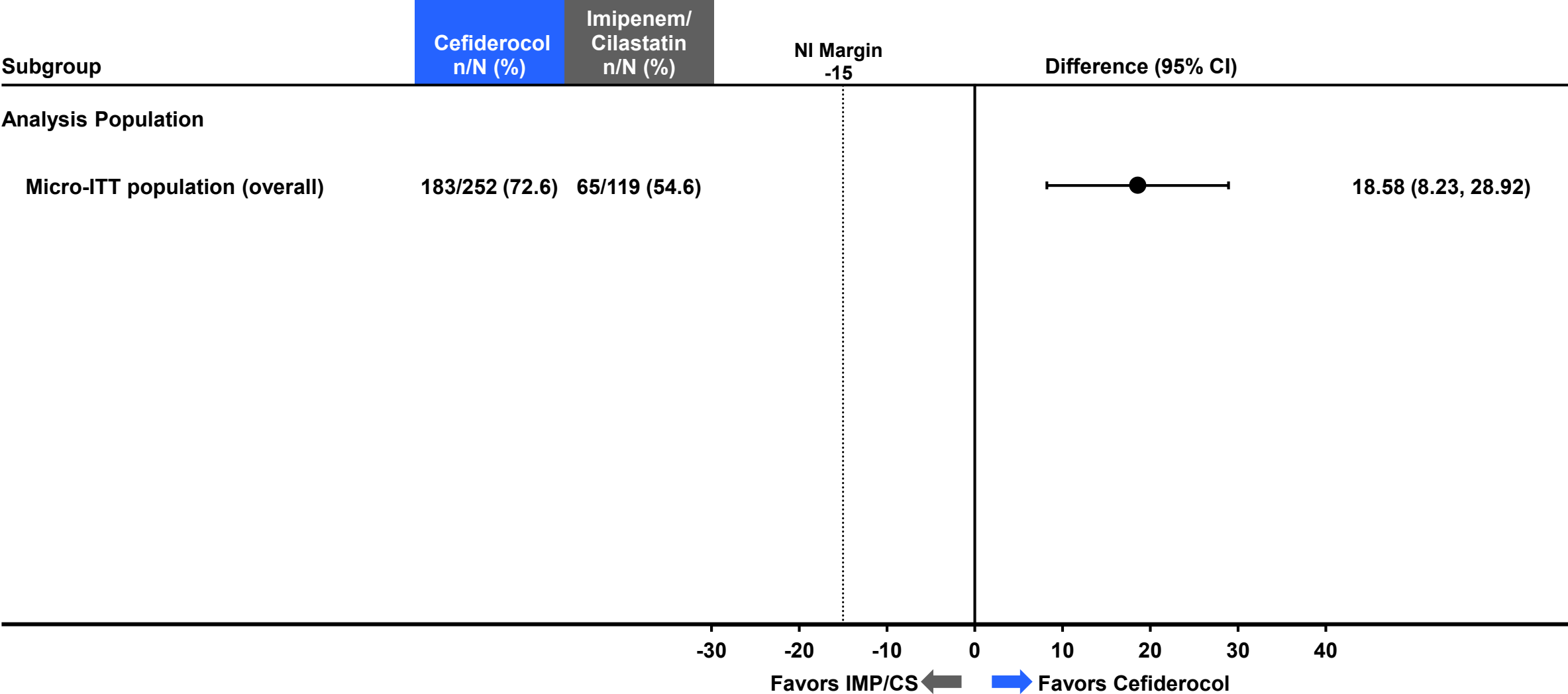
## cUTI Study

### Primary Endpoint Composite Outcome at TOC (Clinical Response and Microbiological Response)



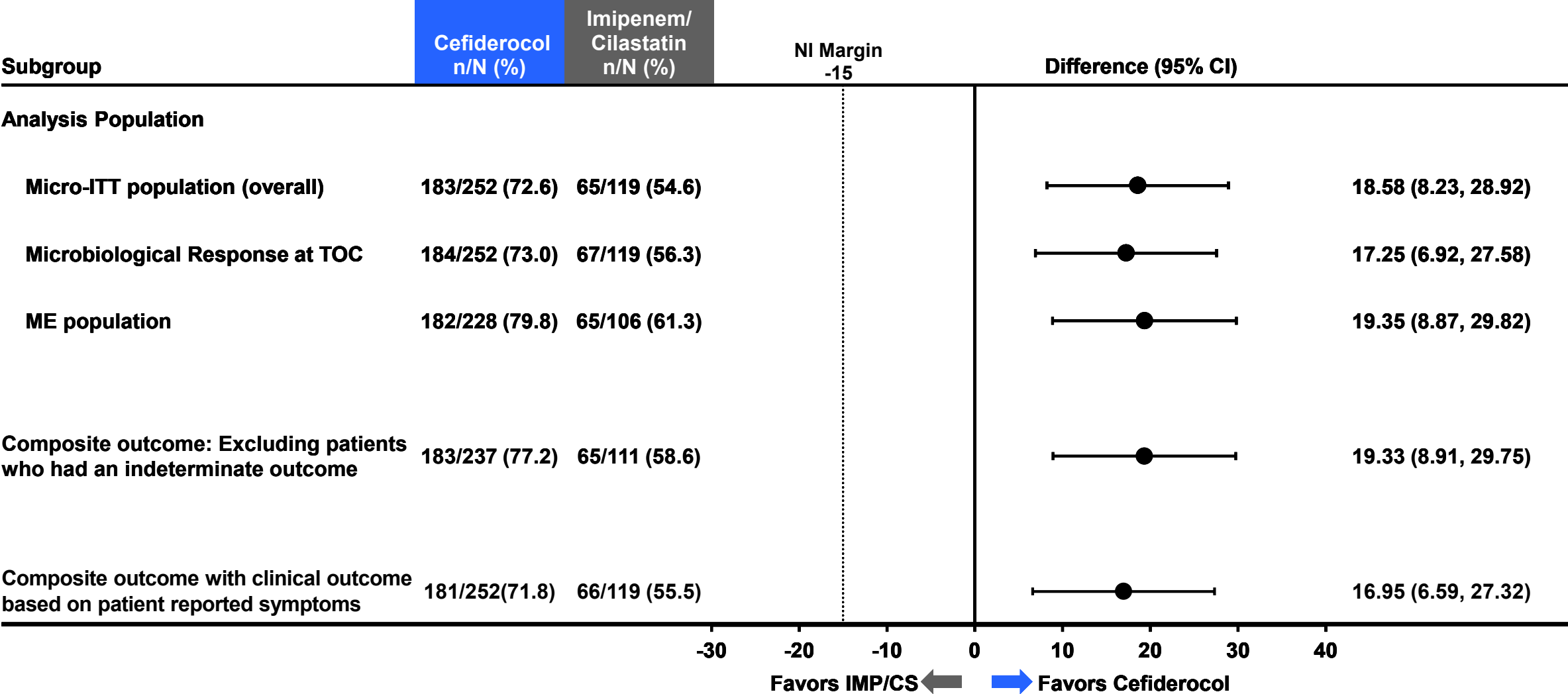
# Composite Endpoint at TOC: Clinical Cure and Micro Eradication

## cUTI Study



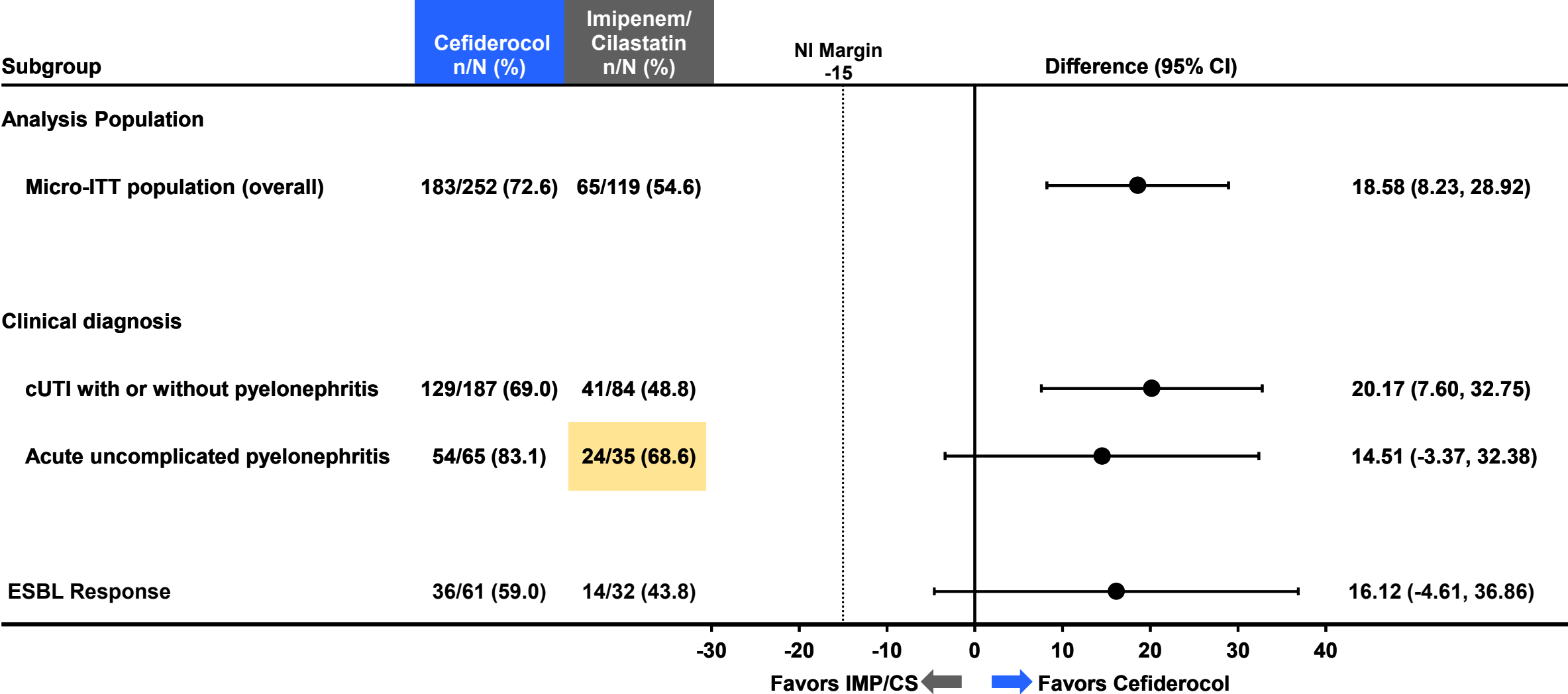
# Composite Endpoint at TOC: Clinical Cure and Micro Eradication

## cUTI Study



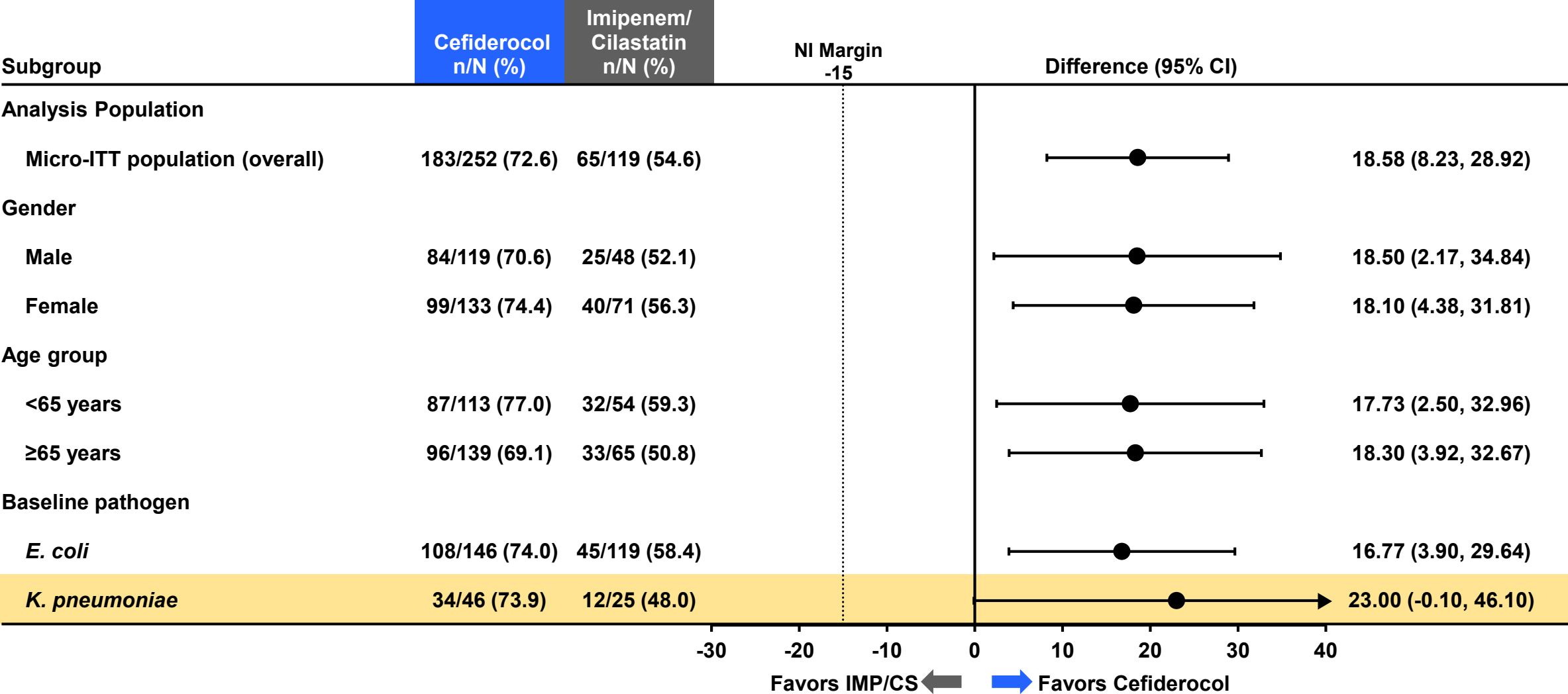
# Composite Endpoint at TOC by Subgroup

## cUTI Study



# Composite Endpoint at TOC: Clinical Cure and Micro Eradication

## cUTI Study



# Composite of Clinical Response and Microbiological Outcome per Pathogen at Test of Cure cUTI Study

Pathogen	Percent Response (n/N)		Treatment Difference
	Cefiderocol	Imipenem/ Cilastatin	
<i>E. coli</i>	74.0 (108/146)	58.4 (45/77)	15.53
<i>K. pneumoniae</i>	73.9 (34/46)	48.0 (12/25)	25.91
<i>P. aeruginosa</i>	46.7 (7/15)	50.0 (2/4)	-3.33
<i>P. mirabilis</i>	69.2 (9/13)	0.0 (0/1)	69.23

# Clinical Responses at Each Time Point

## cUTI Study (Micro-ITT Population)

Clinical Responses	Early Assessment %	End of Treatment %	Test of Cure %	Follow-up %
Cefiderocol	90.5	98.0	89.7	81.3
Imipenem/cilastatin	90.8	99.2	87.4	72.3

# Cefiderocol cUTI Study Efficacy Conclusions

- **Demonstrated non-inferiority to imipenem**
  - Effective both clinically and microbiologically
- **Complicated population at risk for MDR**
- **Consistent across subgroups and pathogens**
- **Sensitivity analyses support primary analysis**
- **The efficacy of cefiderocol supports its use for the treatment of cUTI**

# cUTI Safety

**Simon Portsmouth, MD, FRCP**

Executive Medical Director  
Shionogi Inc.

# Drug Exposure and Safety Overview

## cUTI Study

Safety Population	Cefiderocol N=300	Imipenem/Cilastatin N=148
Completed all study visits	94.3%	93.2%
Duration of exposure, median days (range)	9.0 (1-15)	9.0 (2-15)
Patients with AEs	40.7%	51.4%
Patients with drug-related AEs	9.0%	11.5%
Patients discontinuing due to AEs	1.7%	2.0%
Patients with SAEs	4.7%	8.1%
Patients who died	0.3%	0%

# Adverse Events with an Incidence >2%

## cUTI Study (Safety Population)

	Cefiderocol N=300 %	Imipenem/Cilastatin N=148 %
Diarrhea	4.3	6.1
Hypertension	4.3	5.4
Constipation	3.3	4.1
Infusion site pain	3.0	3.4
Headache	2.3	5.4
Nausea	2.3	4.1
Cough	2.3	0.7
Vomiting	2.0	1.4
Hypokalemia	1.7	2.7
Insomnia	1.3	2.0
Renal cyst	1.3	3.4
Infusion site erythema	1.0	2.0
Abdominal pain upper	0.7	3.4
Cardiac failure	0.7	2.0
<i>C. difficile</i> colitis	0.3	2.7
Vaginal infection	0.3	2.0

# Serious Adverse Events

## cUTI Study

- **SAEs**
  - Cefiderocol: 4.7%
  - Imipenem: 8.1%
- **One SAE reported in more than one patient**
  - *C. difficile* colitis in 2 imipenem patients
- **The only SAE considered treatment related was one occurrence of *C. difficile* diarrhea in cefiderocol arm**
- **No pattern of SAEs**

# One Death

## cUTI Study

- **76-year-old with a medical history of extrapyramidal disorder (was taking levodopa), insulin-dependent diabetes, cerebrovascular disorder, previous stroke, chronic kidney disease, and epilepsy**
- **ECGs done on Day 1 and Day 6 were reported to have had no significant abnormalities and there was no QTc prolongation**
- **The patient had cUTI without pyelonephritis, was bacteremic, and was treated with cefiderocol until Day 7, when it was reported that the patient had a cardiorespiratory arrest and died. There had been no subjective complaints of any problems leading up to this**

# Adverse Events Characteristic of Beta-lactam Class of Antibiotics

## cUTI Study

- **No anaphylaxis**
- **No Hy's law or drug-induced liver injury**
- **One seizure in epileptic patient receiving cefiderocol**
  - Patient had history of seizures
  - Cefiderocol treatment continued without additional seizures
- **One 'hypersensitivity' in patient receiving cefiderocol**
  - Itching only
  - Discontinued after first dose

# Exploratory Markers: Iron Homeostasis

## cUTI Study

- **No differences between treatment groups in markers of iron homeostasis during the study**
  - Serum iron
  - Transferrin saturation
  - Hemoglobin
  - Hematocrit
  - Total iron binding capacity
  - Hepcidin (decreased in both groups)

# Change in MIC to Cefiderocol

## cUTI Study

- **Monitored for increases in cefiderocol MIC values over the course of the study**
  - 7 patients had  $\geq 4$ -fold increases in cefiderocol MIC from baseline
  - The highest MIC was 1  $\mu\text{g/mL}$  at Follow Up in a patient with *E. coli* (0.25  $\mu\text{g/mL}$  at baseline)
  - No bacteria isolated at baseline developed resistance to cefiderocol
- **One of the 7 was a *P. aeruginosa* isolate at Follow Up with MIC 8, and was not present at baseline**

# Safety Conclusions

## cUTI Study

- **Cefiderocol is generally safe and well-tolerated**
- **Has a cephalosporin-like safety profile**
- **No adverse events unique to cefiderocol**
- **No iron homeostasis AEs**
- **Supports use in cUTI in elderly population with comorbidities and at risk of MDR**

# Other Cefiderocol Studies

**CREDIBLE-CR**

**APEKS-NP**

# CREDIBLE-CR Study

**Multicenter, Randomized, Open-Label Study of Cefiderocol or Best Available Therapy (BAT) for Treatment of Severe Infections Caused by Carbapenem-Resistant Gram-negative Pathogens**

# Eligibility

## CREDIBLE-CR Study

- **Eligibility: Identification of Gram-negative pathogen with evidence of carbapenem resistance**
  - Susceptibility testing showing carbapenem resistance (CR)
  - Rapid diagnostic tests (PCR: polymerase chain reaction)
  - Surveillance culture (same infection site)
- **3 infection types**
  - HAP/VAP/HCAP (50%)
  - Bloodstream infection/sepsis (31%)
  - cUTI (19%)

# Patient Population

## CREDIBLE-CR Study

- **BSI/sepsis included bacteremia and non-bacteremic sepsis from any infections other than HAP/VAP/HCAP and cUTI**
- **Exclusions were meningitis, osteomyelitis, endocarditis and patients with cystic fibrosis**
- **Patients often in such end-of-life care with severe comorbidities and long-term hospitalization/ventilation such as:**
  - Decompensated end-stage liver disease
  - Metastatic cancer
  - Inoperable esophageal perforation
  - TEN (Stevens-Johnson syndrome)
  - 56% burns with smoke inhalation
  - Shock prior to and at randomization
  - Major trauma with head injury
  - Ischemic bowel with perforation

# Stratification

## CREDIBLE-CR Study

- **Patients were stratified according to infection type, APACHE II score, and geographic region**
- **Not stratified by pathogen or other severity indicators such as:**
  - Mechanical ventilation status
  - Shock
  - Location in ICU

# Primary Study Objectives

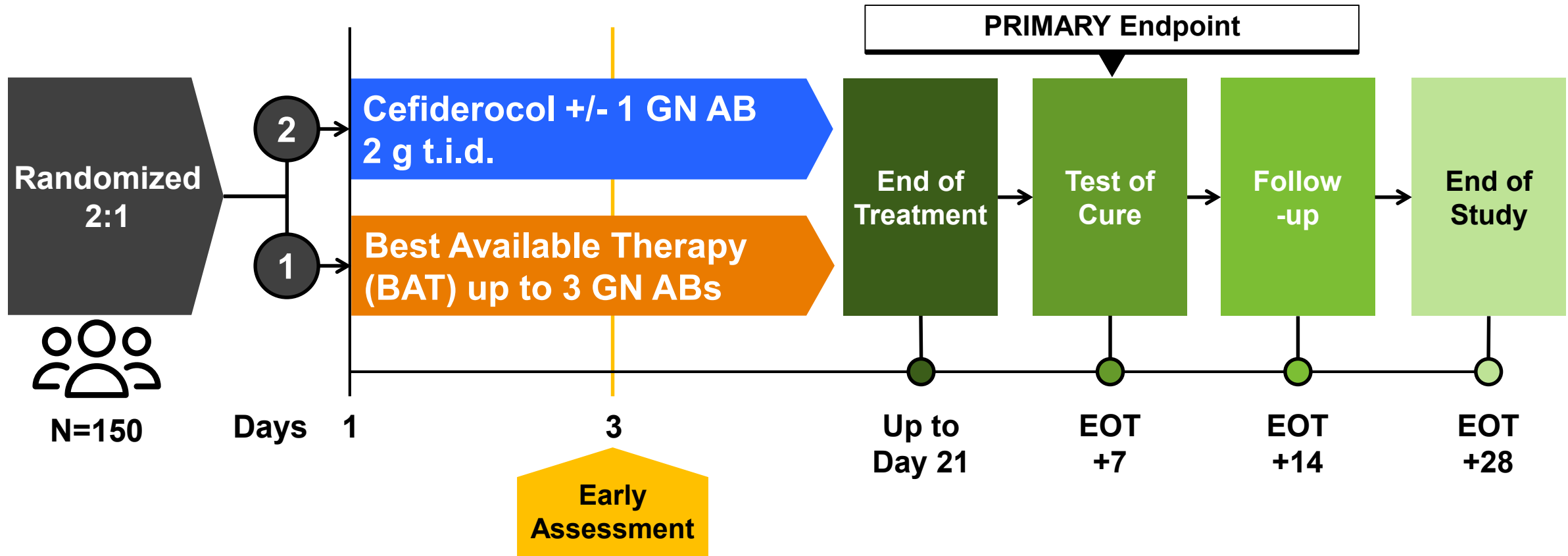
## CREDIBLE-CR Study

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- **Clinical and microbiological outcomes – efficacy in treatment of serious life-threatening carbapenem-resistant Gram-negative infections**
- **Study collected detailed patient-level information**
- **Study was designed without inferential testing of a hypothesis**

# Study Schematic

## CREDIBLE-CR Study

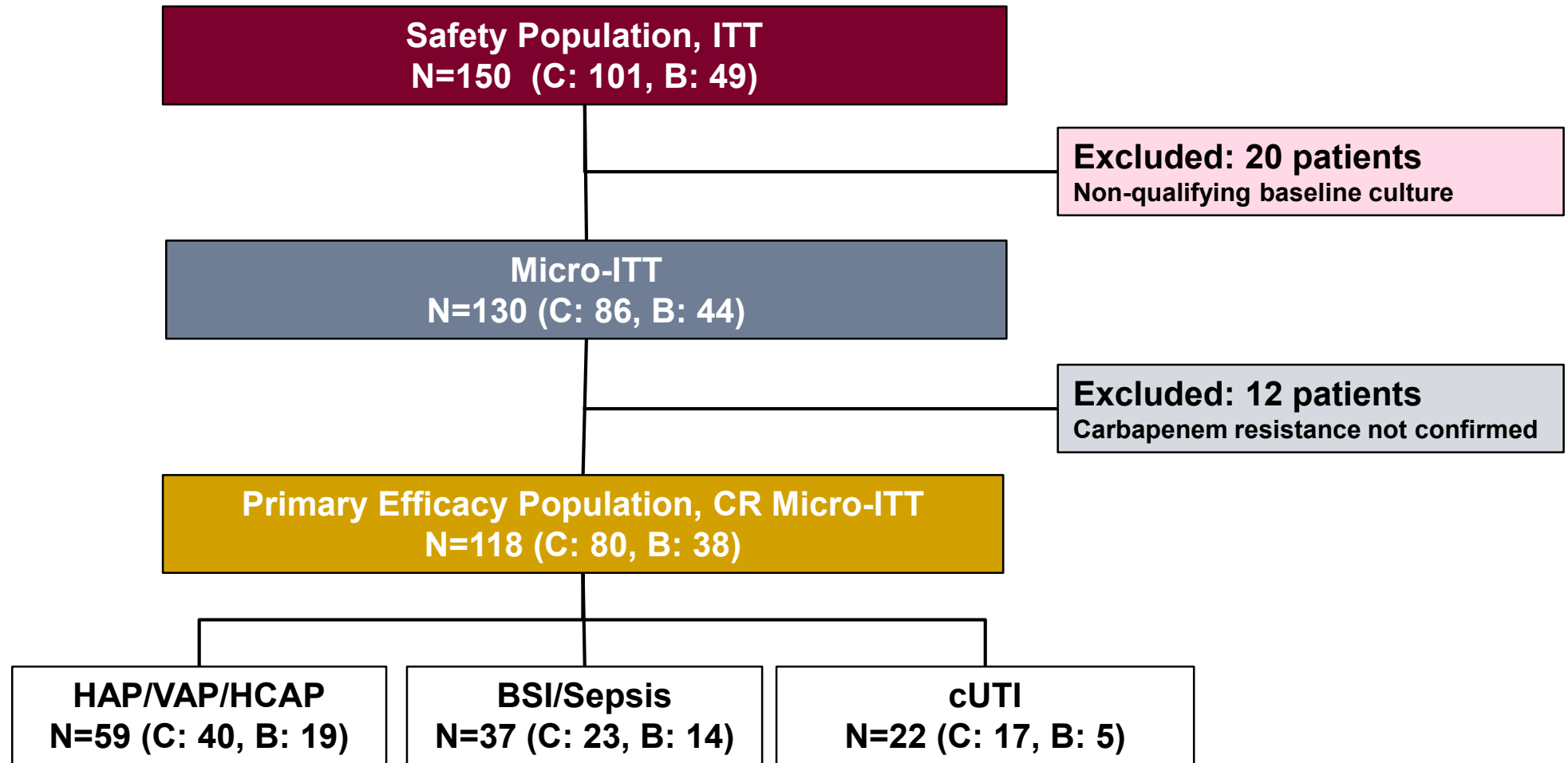


- **Primary Endpoint at Test of Cure**

- HAP/VAP/HCAP and Bloodstream Infections/Sepsis – Clinical outcome
- cUTI – Microbiological outcome

# Patient Population and Disposition

## CREDIBLE-CR Study



# Baseline Characteristics

## CREDIBLE-CR Study (Safety Population)

Parameter		Cefiderocol n=101	BAT n=49
Sex, (%)	Men (%)	65.3	71.4
	Median	69.0 (19, 92)	62.0 (19, 92)
Age, y	≥65, (%)	63.4	44.9
	Median (min, max)	59.2 (9.4, 539.6)	69.4 (4.6, 270.8)
CrCl, mL/min	Median (min, max)	59.2 (9.4, 539.6)	69.4 (4.6, 270.8)
CrCl renal grading group in mL/min, n (%)	<50 (Moderate and Severe) (%)	42.6	30.6
	HAP/VAP/HCAP (%)	44.6	44.9
Clinical diagnosis at baseline, n (%)	BSI/sepsis (%)	29.7	34.7
	cUTI (%)	25.7	20.4
APACHE II score	Median (min, max)	15 (2, 29)	14 (2, 28)
Sequential Organ Failure Assessment Score	Median (min, max)	4.0 (0, 17)	4.0 (0, 16)
Clinical Pulmonary Infection Score	Median (min, max)	5.0 (2, 9)	5.0 (0, 7)

# Baseline CR Gram-negative Pathogens

## CREDIBLE-CR Study (CR Micro-ITT Population)

Diagnosis Pathogen	Cefiderocol N=80 %	BAT N=38 %
CR <i>A. baumannii</i>	46.3	44.7
CR <i>K. pneumoniae</i>	33.8	31.6
CR <i>P. aeruginosa</i>	15.0	26.3
<i>S. maltophilia</i>	6.3	0

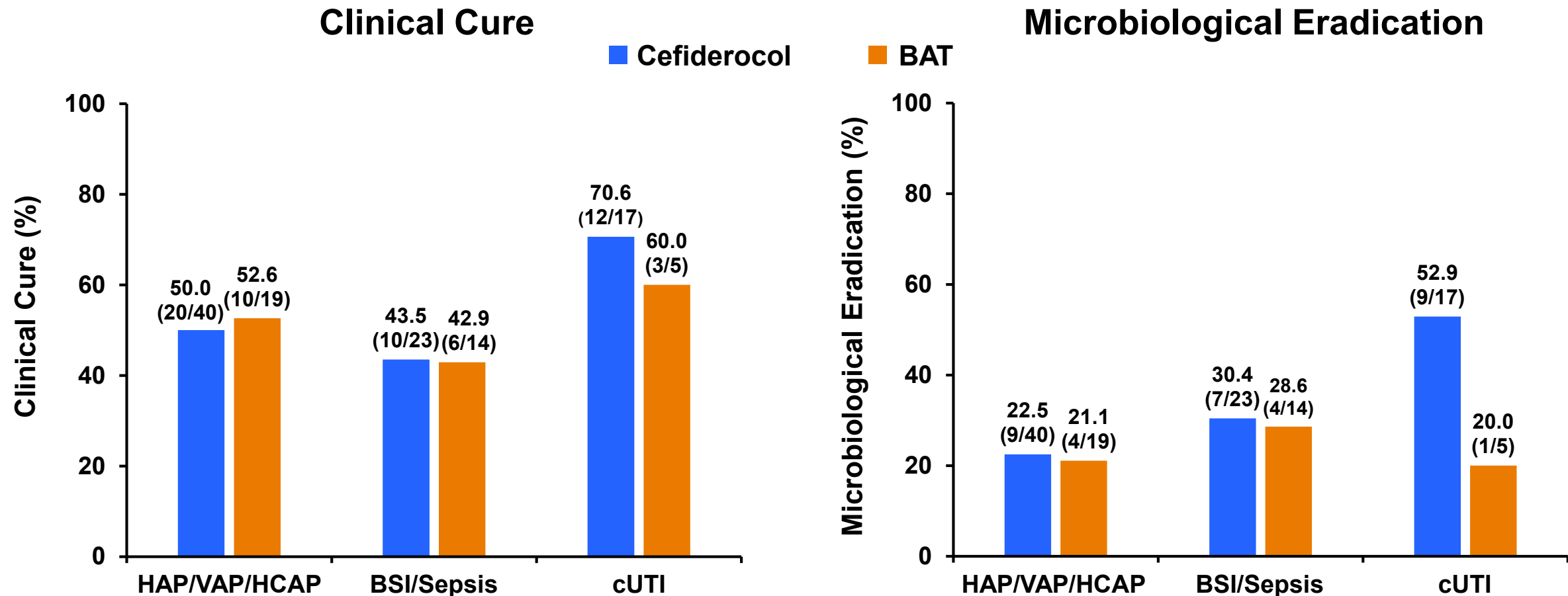
# Study Drug Regimen

CREDIBLE-CR Study (CR Micro-ITT Population)

Cefiderocol N=80		BAT N=38	
Gram-negative Regimen	%	Gram-negative Regimen	%
Cefiderocol monotherapy	82.5	Monotherapy	28.9
		Colistin	15.8
		Non-colistin	13.2
Cefiderocol + one adjunctive Gram-negative antibiotic	17.5	Combination therapy	71.1
		Colistin-based	50.0
		Non-colistin based	21.1
		Total Colistin Based	65.8

# Outcomes at TOC by Clinical Diagnosis

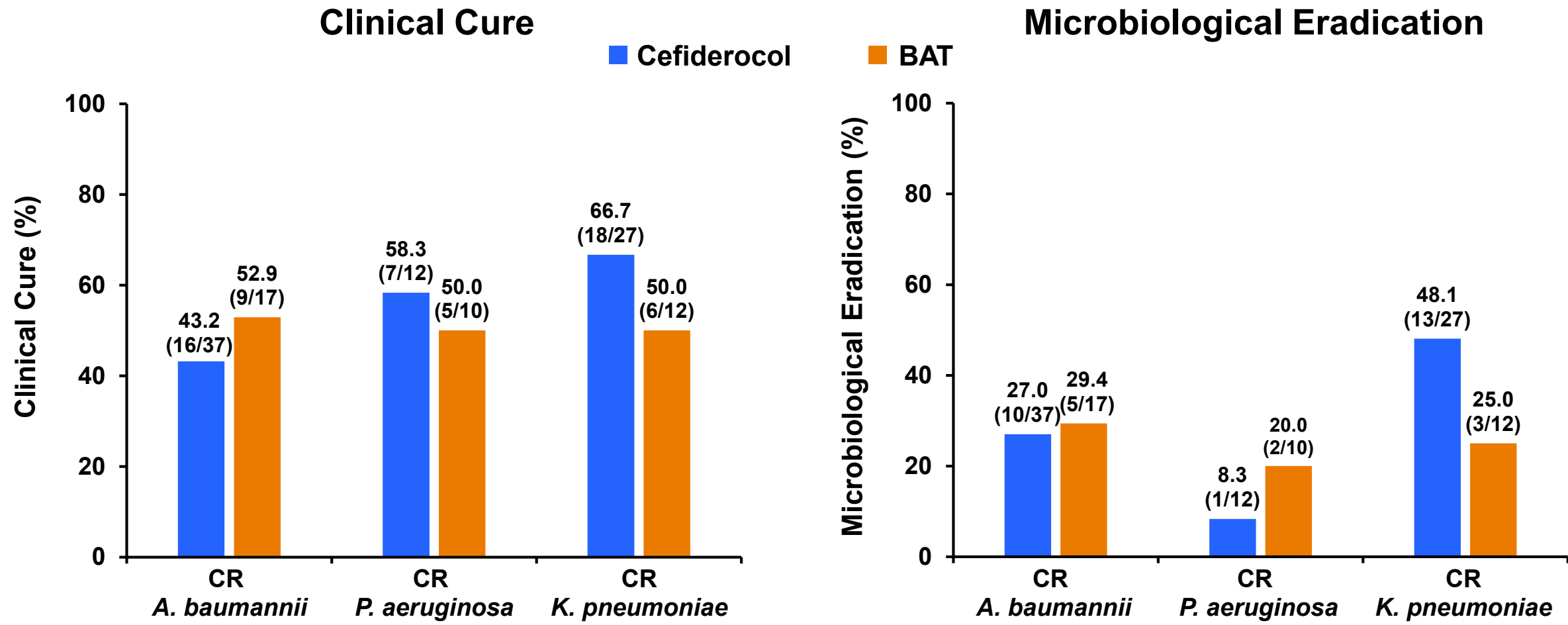
## CREDIBLE-CR Study (CR Micro-ITT Population)



BAT = best available therapy; BSI = bloodstream infection; cUTI = complicated urinary tract infection; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; VAP = ventilator-associated pneumonia; TOC = test of cure

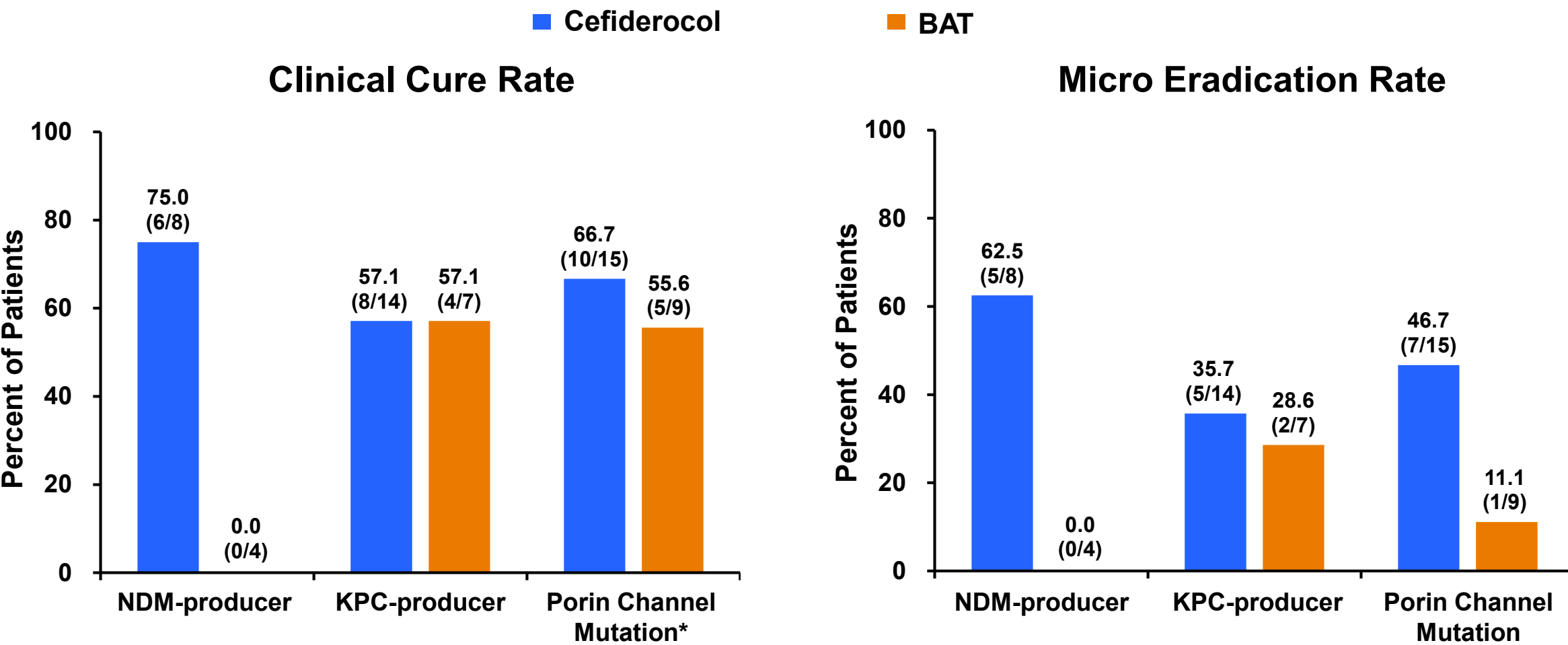
# Outcomes at TOC by Baseline Pathogen

CREDIBLE-CR Study (CR Micro-ITT Population)



# Clinical and Microbiological Outcomes at TOC in Enterobacteriaceae by Carbapenemase or Porin Channel Mutation

CREDIBLE-CR Study (CR Micro-ITT Population)

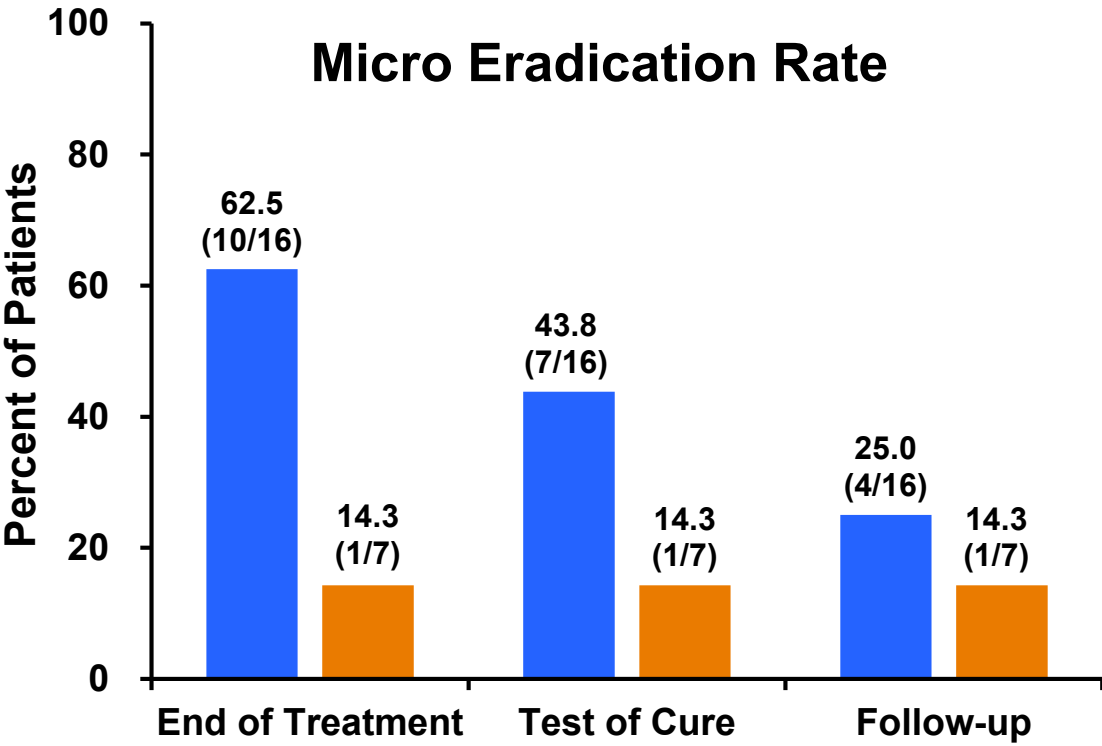
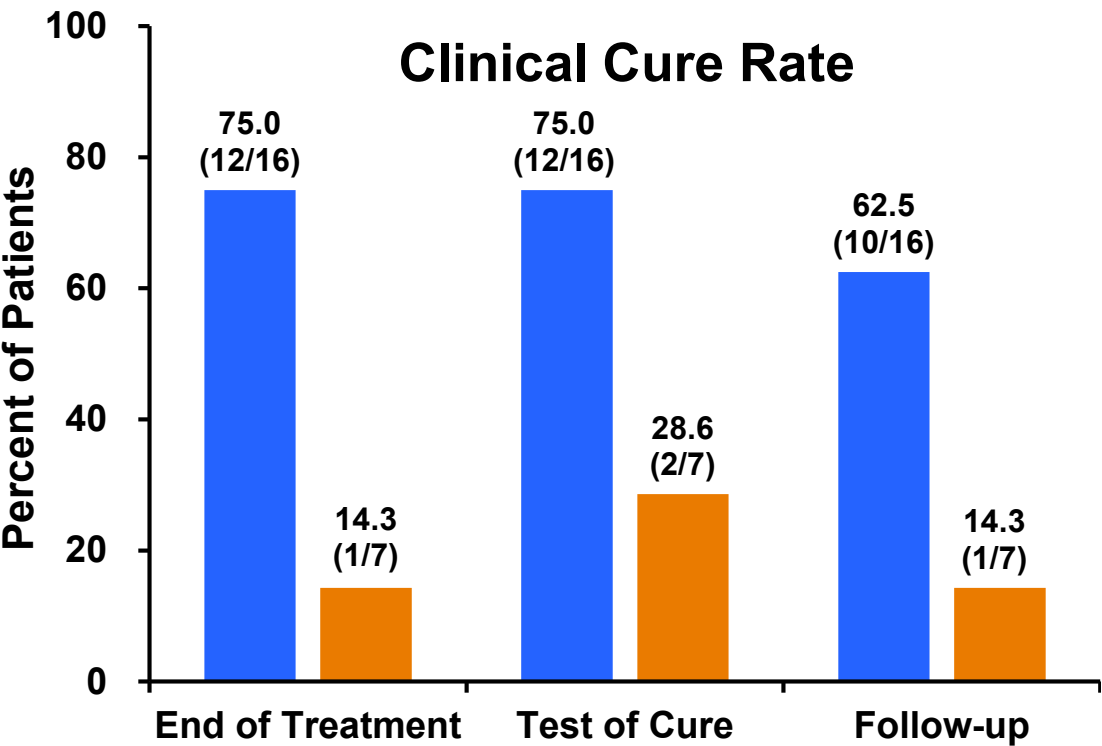


\*OMPK35/36-deficient  
Only patients with molecular data are included.

# Clinical and Micro Outcomes in Metallo Beta-lactamase Producing Gram-negative Pathogens

CREDIBLE-CR Study (CR Micro-ITT Population)

Cefiderocol (N=16)      BAT (N=7)



# Safety in the CREDIBLE-CR Study

# Adverse Events

## CREDIBLE-CR Study (Safety Population)

AE Category	Cefiderocol N=101		BAT N=49	
	Patients n (%)	AEs n'	Patients n (%)	AEs n'
<b>AEs</b>	<b>92 (91.1)</b>	<b>634</b>	<b>47 (95.9)</b>	<b>311</b>
<b>Treatment-related AEs</b>	<b>15 (14.9)</b>	<b>27</b>	<b>11 (22.4)</b>	<b>16</b>
<b>SAEs</b>	<b>50 (49.5)</b>	<b>92</b>	<b>23 (46.9)</b>	<b>36</b>
<b>Treatment-related SAEs</b>	<b>1 (1.0)</b>	<b>1</b>	<b>5 (10.2)</b>	<b>7</b>
<b>Discontinuation due to AEs</b>	<b>10 (9.9)</b>	<b>12</b>	<b>3 (6.1)</b>	<b>3</b>
<b>Discontinuation due to treatment-related AEs</b>	<b>3 (3.0)</b>	<b>3</b>	<b>2 (4.1)</b>	<b>2</b>
<b>AEs leading to death</b>	<b>34 (33.7)</b>	<b>45</b>	<b>9 (18.4)</b>	<b>14</b>

# ALT and Bilirubin: Patient #3 (FDA Patient #5)

## CREDIBLE-CR Study (Safety Population)

- **Patient with chronic HBV and prior liver failure**
  - Hepatic failure on admission
  - *K. oxytoca*, *K. pneumoniae* HAP and treated with pip-tazo Day -4 until Day 1
  - Developed fulminant hepatic failure Day 2 and GI bleed. Anasarca due to hypoalbuminemia (bilirubin 5.13)
- **Completed cefiderocol on Day 9 (clinical cure at TOC)**
- **Died 26 days after EOT (Day 35) of refractory hepatic failure**

# **ALT and Bilirubin: Patient #5 (FDA Patient #26)**

## **CREDIBLE-CR Study (Safety Population)**

- **Multiple trauma including liver laceration (baseline TBL 4.55 mg/dL)**
  - Serious hyponatremia on Day 1 and cefiderocol was discontinued
  - Bilirubin increased on Day 5
- **Completed cefiderocol on Day 2 (after 3 doses)**
- **Died on Day 6 of multiple trauma and skull fracture**

# Renal Safety

## CREDIBLE-CR Study (Safety Population)

- **Comparator primarily colistin**
- **Baseline abnormalities in both groups (prior colistin and renal failure), baseline CrCl lower in cefiderocol treated patients**

# Change in Renal Function by Treatment Group

## CREDIBLE-CR Study (Safety Population)

Serum Creatinine Change from Baseline	Cefiderocol %	BAT %
1.5 to 2 times increase	14.9	14.3
2 to 3 times increase	5.0	16.3
> 3 times increase	1.0	4.0

# Adverse Events

## CREDIBLE-CR Study (Safety Population)

AE Category	Cefiderocol N=101		BAT N=49	
	Patients n (%)	AEs n'	Patients n (%)	AEs n'
<b>AEs</b>	<b>92 (91.1)</b>	<b>634</b>	<b>47 (95.9)</b>	<b>311</b>
Treatment-related AEs	15 (14.9)	27	11 (22.4)	16
<b>SAEs</b>	<b>50 (49.5)</b>	<b>92</b>	<b>23 (46.9)</b>	<b>36</b>
Treatment-related SAEs	1 (1.0)	1	5 (10.2)	7
Discontinuation due to AEs	10 (9.9)	12	3 (6.1)	3
Discontinuation due to treatment-related AEs	3 (3.0)	3	2 (4.1)	2
<b>AEs leading to death</b>	<b>34 (33.7)</b>	<b>45</b>	<b>9 (18.4)</b>	<b>14</b>

# Patients with Adverse Events Leading to Death

## CREDIBLE-CR Study (Safety Population)

System Organ Class	Cefiderocol N=101 %	BAT N=49 %
Patients with adverse events	33.7	18.4
Cardiac disorders	5.9	6.1
General disorders and administration site conditions	3.0	6.1
Hepatobiliary disorders	2.0	0
Infections and infestations	20.8	6.1
Metabolism and nutrition disorders	1.0	2.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1.0	0
Renal and urinary disorders	3.0	2.0
Respiratory, thoracic and mediastinal disorders	4.0	4.1
Vascular disorders	1.0	0

## **Hepatobiliary Disorders Leading to Death: Patient #27 (FDA Patient #16)**

**CREDIBLE-CR Study (Safety Population)**

- **HBV and prior hepatic encephalopathy, SBP and bleeding varices**
- **Pulseless cardiac arrest and septic shock Day -4**
- **VAP: *A. nosocomialis*, *P. aeruginosa*, *C. indologenes***
- **Day 1: Worsening liver failure**
- **Day 4: Sputum *A. nosocomialis*, *P. aeruginosa*, *S. maltophilia*, clinical cure**
- **Day 5: Worsening septic shock, DNR**
- **Day 8: Died due to worsening liver failure and septic shock**

# Patients with Adverse Events Leading to Death

## CREDIBLE-CR Study (Safety Population)

System Organ Class	Cefiderocol N=101 %	BAT N=49 %
Patients with adverse events	33.7	18.4
Cardiac disorders	5.9	6.1
General disorders and administration site conditions	3.0	6.1
Hepatobiliary disorders	2.0	0
Infections and infestations	20.8	6.1
Metabolism and nutrition disorders	1.0	2.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1.0	0
Renal and urinary disorders	3.0	2.0
Respiratory, thoracic and mediastinal disorders	4.0	4.1
Vascular disorders	1.0	0

# Infection/Infestation Adverse Events Leading to Death

## CREDIBLE-CR Study (Safety Population)

System Organ Class Preferred Term	Cefiderocol N=101 n (%)	BAT N=49 n (%)
Patients with AEs leading to death	34 (33.7)	9 (18.4)
Infections and infestations	21 (20.8)	3 (6.1)
Bacteremia	2 (2.0)	0
Device-related infection	0	1 (2.0)
Pneumonia	5 (5.0)	0
Pneumonia bacterial	1 (1.0)	0
Sepsis	3 (3.0)	0
Septic shock	11 (10.9)	3 (6.1)

# All-cause Mortality

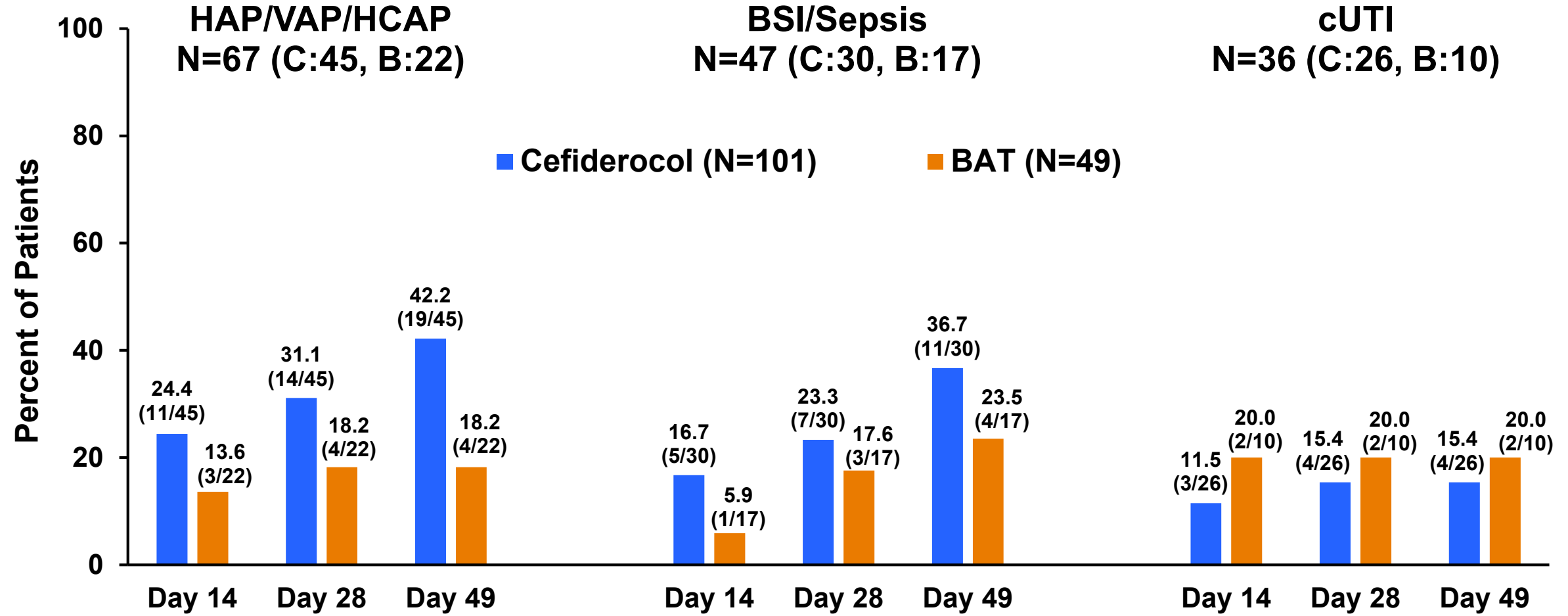
## CREDIBLE-CR Study (Safety Population)

	Cefiderocol % n/N	BAT % n/N	Difference %	95% CI
Day 14	18.8 (19/101)	12.2 (6/49)	6.6	-5.4 to 18.5
Day 28	24.8 (25/101)	18.4 (9/49)	6.4	-7.3 to 20.1
Day 49	33.7 (34/101)	20.4 (10/49)	13.3	-1.3 to 27.8

4 additional deaths in the BAT group and 2 in the cefiderocol group were spontaneously reported after Day 50

# All-cause Mortality Rates by Type of Infection

## CREDIBLE-CR Study (Safety Population)



# Independent Blinded Adjudication of Study Mortality

**CREDIBLE-CR, an Open-label Study**

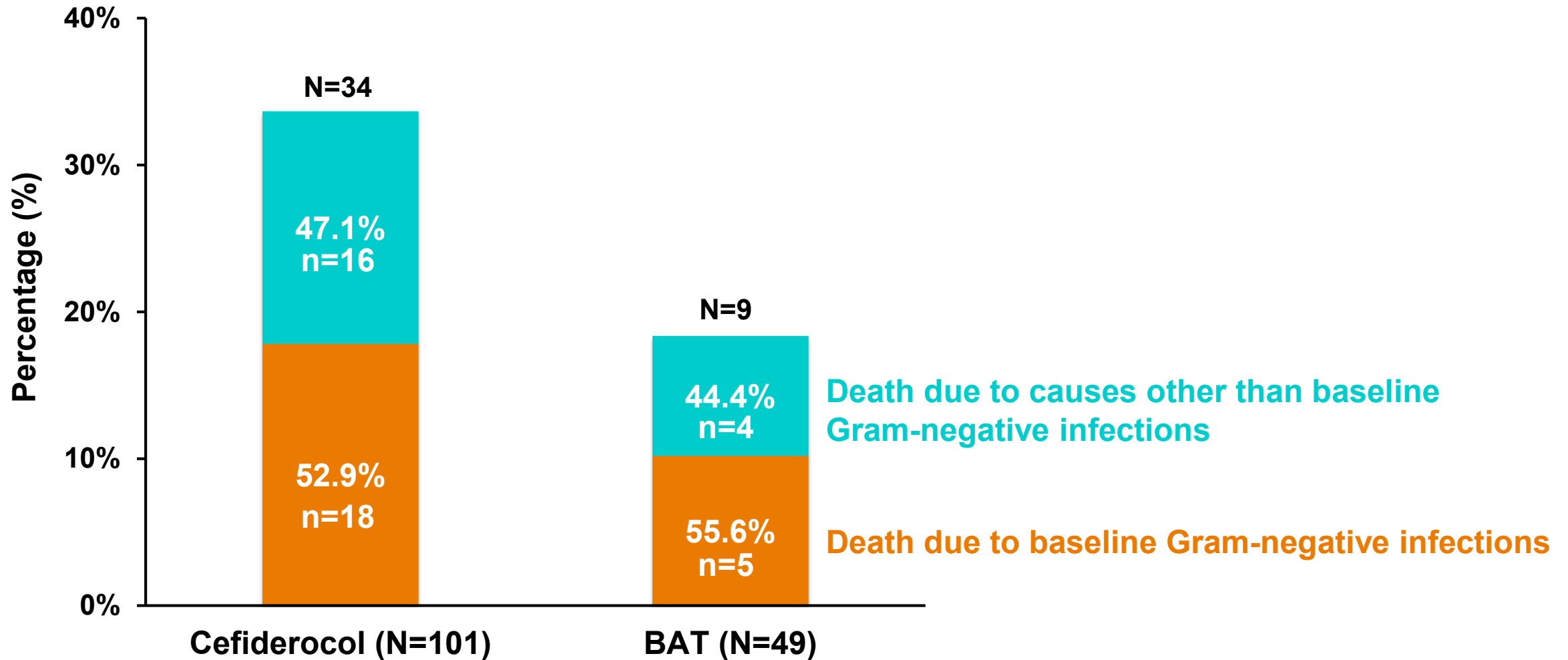
# **Adjudication Committee Makeup and Procedure**

## **CREDIBLE-CR Study**

- **Independent blinded adjudication committee, three members blinded to study treatment and unaware of aggregate results in the trial including the mortality**
- **Death could be assessed as not related to qualifying Gram-negative infection (Category 1) due to:**
  - Comorbidity,
  - Different infection, or
  - Drug related adverse event
- **Death due to qualifying Gram-negative infection, and if so, does this represent a failure of antibiotic treatment (Category 2)**

# Results of Adjudication by Blinded Adjudication Committee

## Treatment-Emergent Death (Safety Population, N=150)



# **CREDIBLE-CR: Sponsor Assessment of Mortality**

- **No toxicology or pre-clinical concerns**
- **Causes of death variable, no discernible pattern suggesting causality**
- **Blinded adjudication confirmed half of deaths in both arms unrelated to Gram-negative infection**
- **Exploratory regression analysis shows no single factor impacts on the observed mortality difference**
- **PK/PD assessment – drug exposure sufficient in plasma and ELF**

# CREDIBLE-CR Mortality Conclusion

- **Heterogeneous population and prognostic factors seem to go both ways and do not predict outcome**
- **No deaths considered to be adverse drug reactions of cefiderocol by investigators, the DSMB or the blinded adjudication committee**
- **All-cause mortality difference in this critically-ill population is difficult to assess and could be due to chance**

# **Pneumonia Evaluation in CREDIBLE-CR and APEKS-NP**

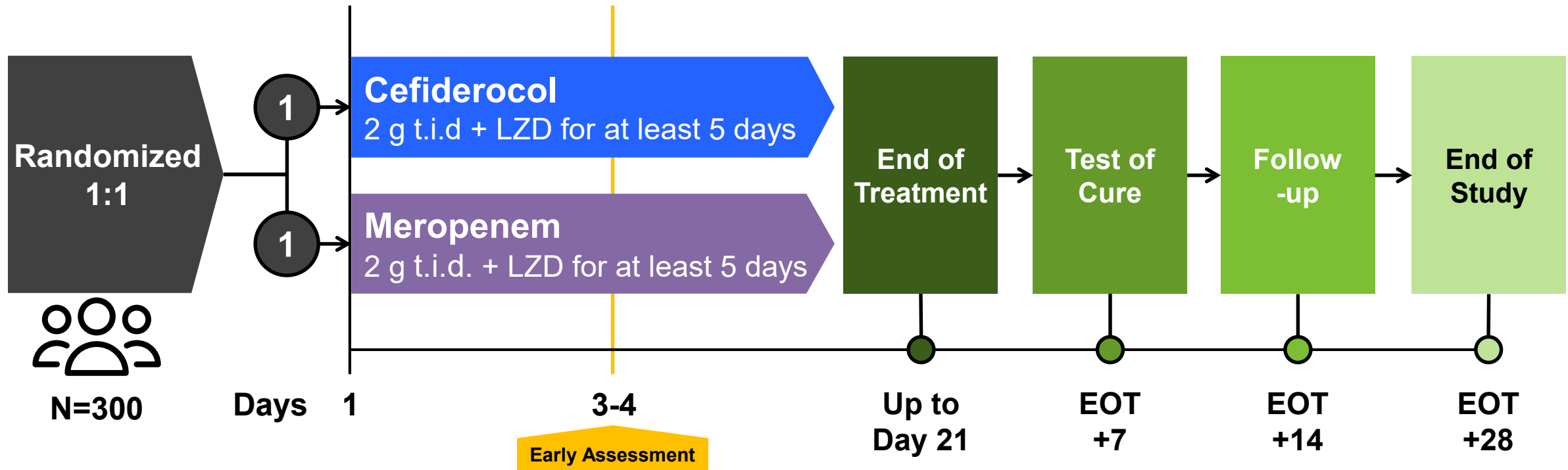
- **50% of CR Micro-ITT population in CREDIBLE-CR had nosocomial pneumonia (HAP/VAP/HCAP)**
- **Shionogi recently completed a randomized double-blind cefiderocol study in HAP/VAP/HCAP – APEKS-NP**

# APEKS-NP Study

**Double-Blind RCT of Cefiderocol Compared with High-Dose Meropenem in HAP/VAP/HCAP Caused by Gram-negative Pathogens**

# Study Design

## APEKS-NP Study



- **Primary Endpoint**
  - All-cause mortality at Day 14 in modified ITT population

# Patient Demographics and Baseline Characteristics

## APEKS-NP Study (ITT Population)

Baseline Characteristics Statistic/Category	Cefiderocol N=148 %	Meropenem N=150 %
Gender (Male)	68.2	69.3
Age (Mean)	64.7	65.6
≥75 years	27.0	31.3
<75 years	73.0	68.7
Clinical diagnosis		
HABP	40.5	40.7
VABP	40.5	43.3
HCABP	18.9	16.0
Ventilation status at randomization		
Ventilated	61.5	58.0
APACHE II score		
≤15	50.7	52.0
≥16	49.3	48.0

# Baseline Characteristics: Top 5 Baseline Gram-negative Pathogens

APEKS-NP Study (ITT Population)

Baseline Characteristics Statistic/Category	Cefiderocol N=148 n (%)	Meropenem N=150 n (%)
Top 5 baseline Gram-negative pathogens		
<i>K. pneumoniae</i>	32.4	29.3
<i>P. aeruginosa</i>	16.2	16.0
<i>A. baumannii</i>	15.5	16.0
<i>E. coli</i>	12.8	14.7
<i>E. cloacae</i>	4.7	5.3

# All-cause Mortality

## APEKS-NP Study (Modified-ITT Population)

Timepoint	Cefiderocol % n/N'	Meropenem % n/N'	Treatment Comparison	
			Difference %	95% CI
Day 14 (Primary Endpoint)	12.4 18/145	11.6 17/146	0.8	-6.6, 8.2
Day 28	21.0 30/143	20.5 30/146	0.5	-8.7, 9.8
Day 49	27.5 39/142	25.3 37/146	2.2	-7.8, 12.3

# Overall Summary of Clinical Studies

- **Efficacy demonstrated in two double-blind clinical trials**
  - APEKS-cUTI study
    - Non-inferiority with results consistent with superiority
  - APEKS-NP study
    - Non-inferior to high-dose extended-infusion meropenem
    - 14-Day and 28-Day all-cause mortality similar – 60% mechanically ventilated
- **Mortality difference seen in the CREDIBLE-CR study**
  - Extensively investigated with no definitive explanation

# Benefit/Risk of Cefiderocol for cUTI

**David Paterson, MBBS, PhD**

Infectious Diseases Physician, Royal Brisbane and Women's Hospital

Director, University of Queensland of Queensland Centre for Clinical Research

Brisbane, Australia

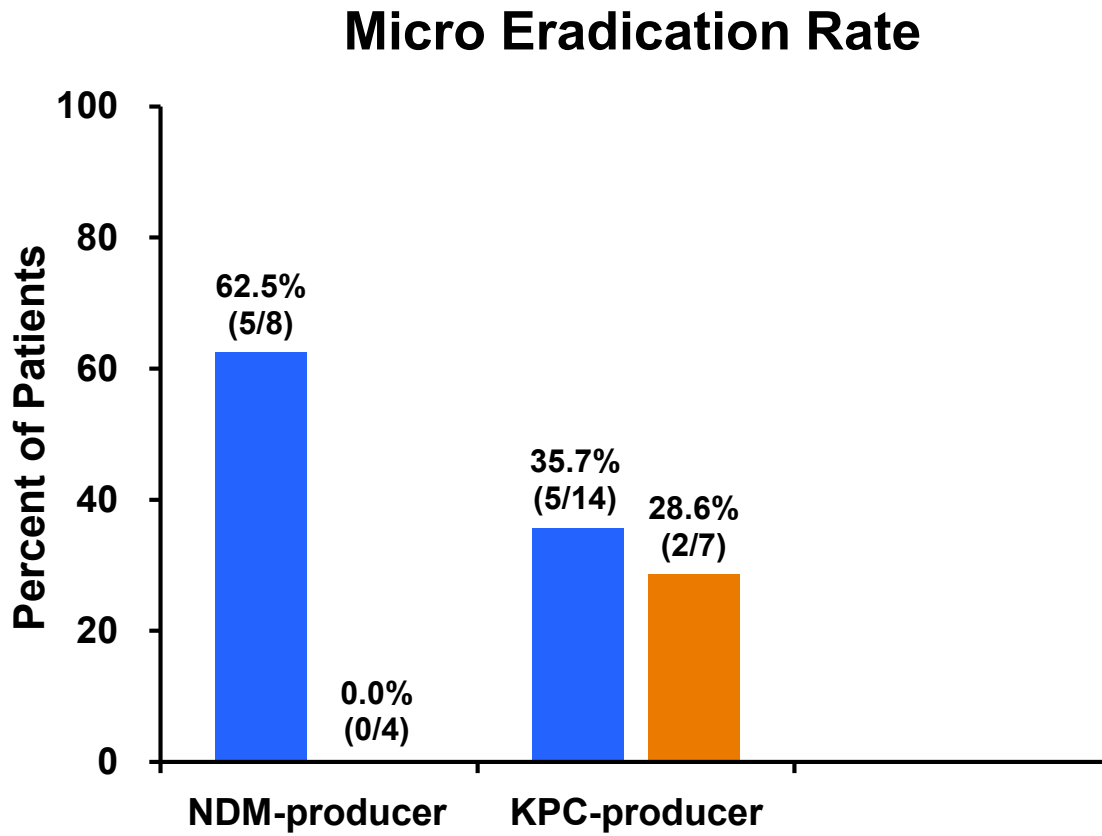
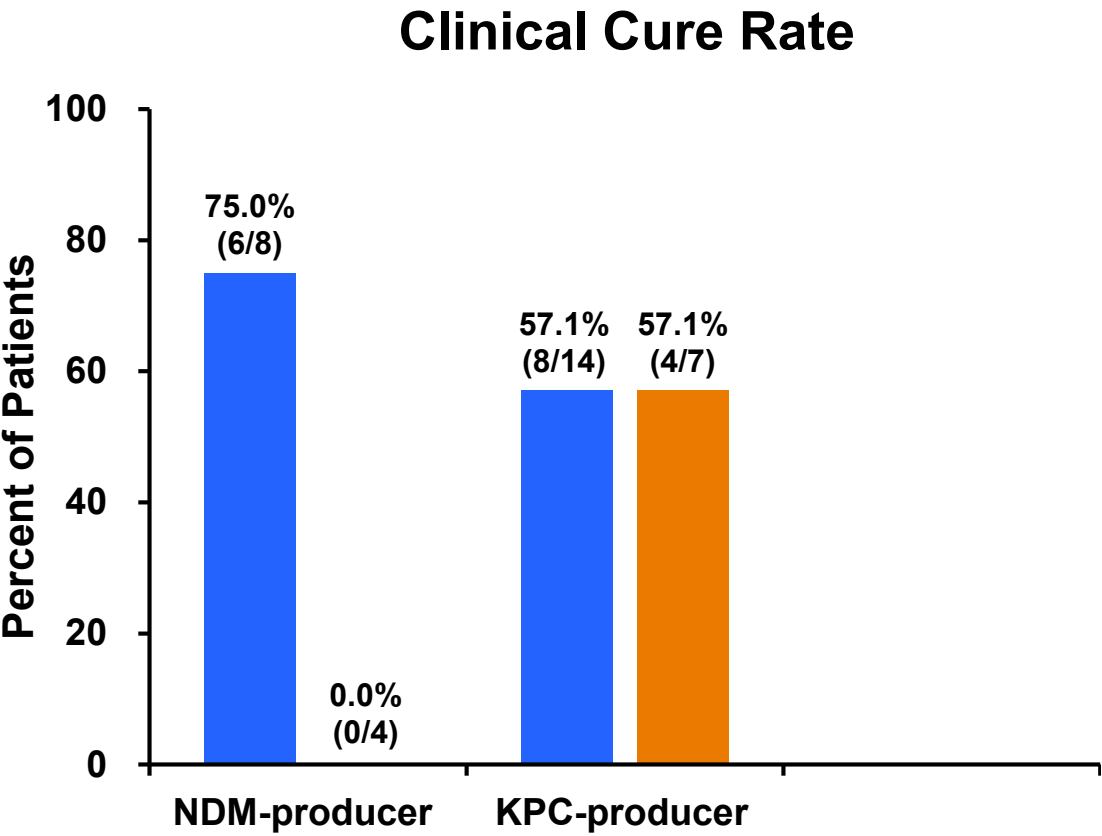
# Treating cUTI Patients Infected with Carbapenem-resistant Pathogens

- **Generally not otherwise healthy patients**
- **Healthcare-associated infections**
  - Examples: Post cancer treatment or organ transplant
  - Multiple prior courses of antibiotics
- **Typically carbapenem-resistant Enterobacteriaceae and occasionally *Pseudomonas***
- **Faced with few options**
  - Inactivity of new beta-lactam/beta-lactamase inhibitor combinations if due to metallo beta-lactamases (eg, NDM, VIM, or IMP)

# Clinical and Microbiological Outcomes at TOC in Enterobacteriaceae by Carbapenemases

CREDIBLE-CR Study (CR Micro-ITT Population)

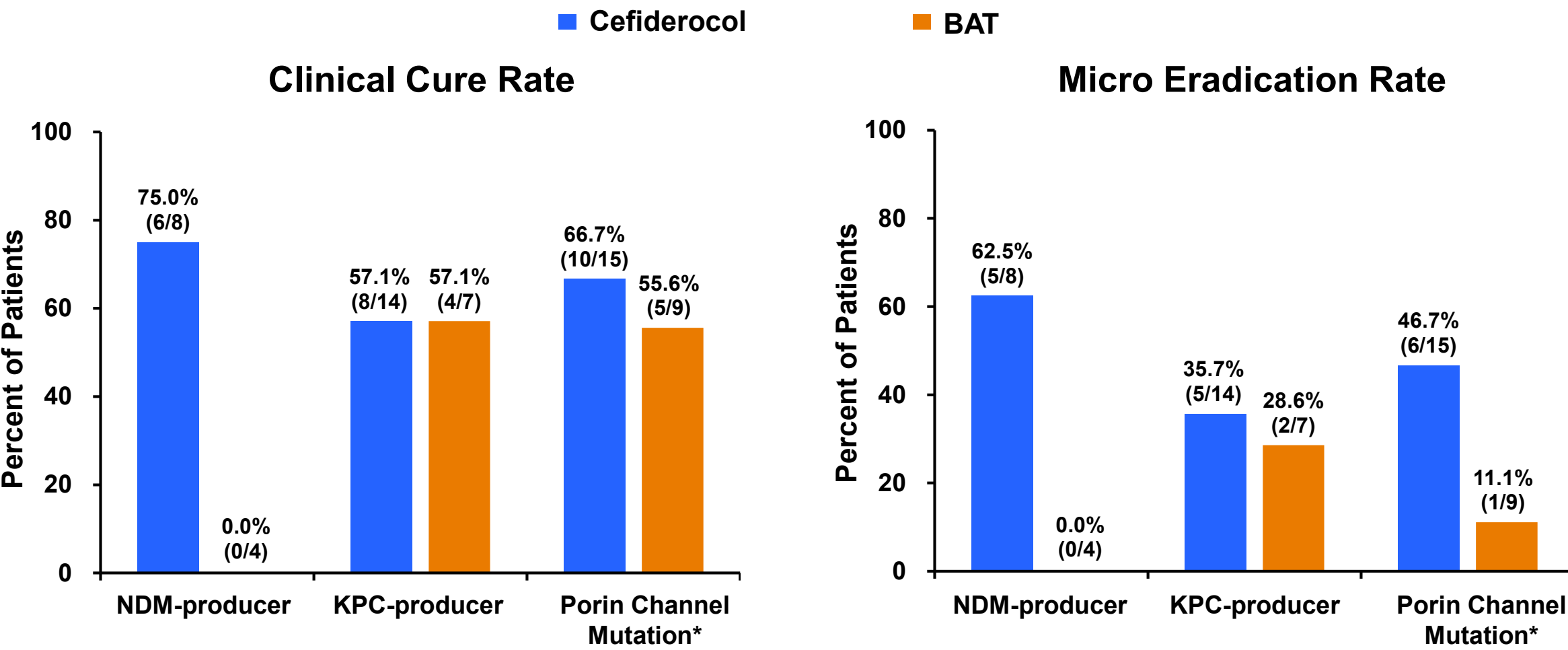
Cefiderocol BAT



Only patients with molecular data are included.

# Clinical and Microbiological Outcomes at TOC in Enterobacteriaceae by Carbapenemases or Porin Channel Mutation

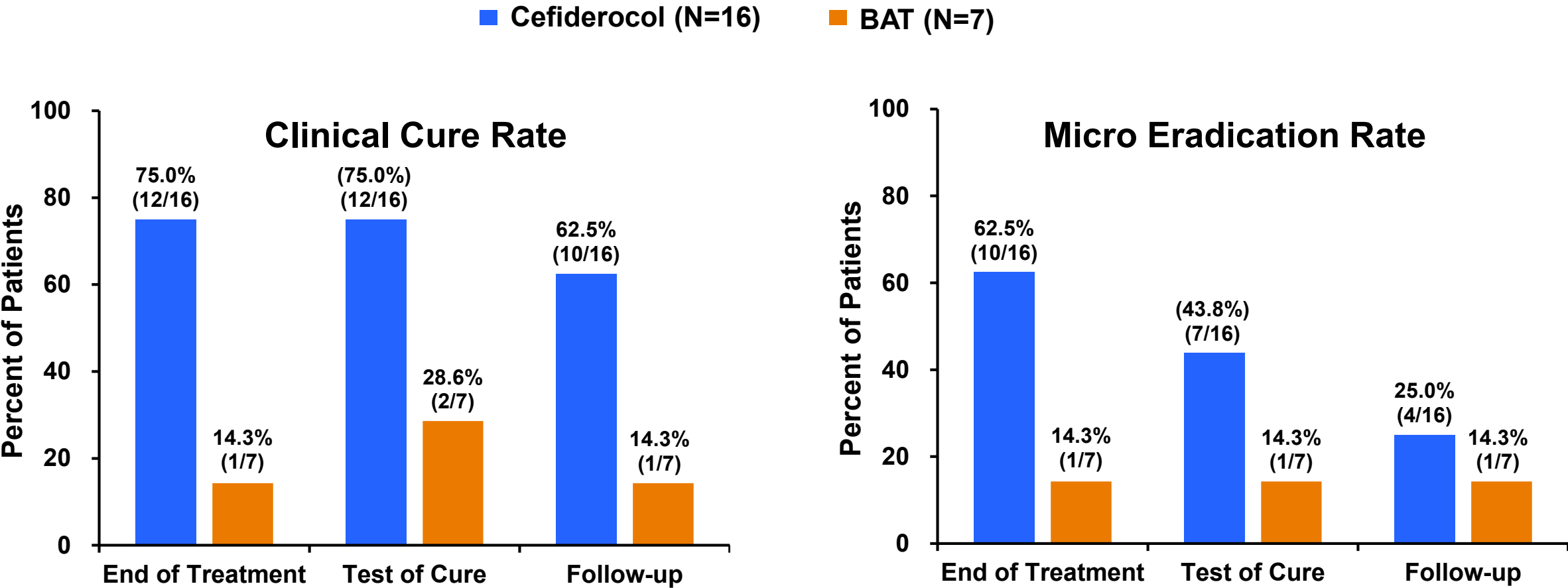
CREDIBLE-CR Study (CR Micro-ITT Population)



\*OMPK35/36-deficient  
Only patients with molecular data are included.

# Clinical and Micro Outcomes in Metallo Beta-lactamase Producing Gram-negative Pathogens

CREDIBLE-CR Study (CR Micro-ITT Population)

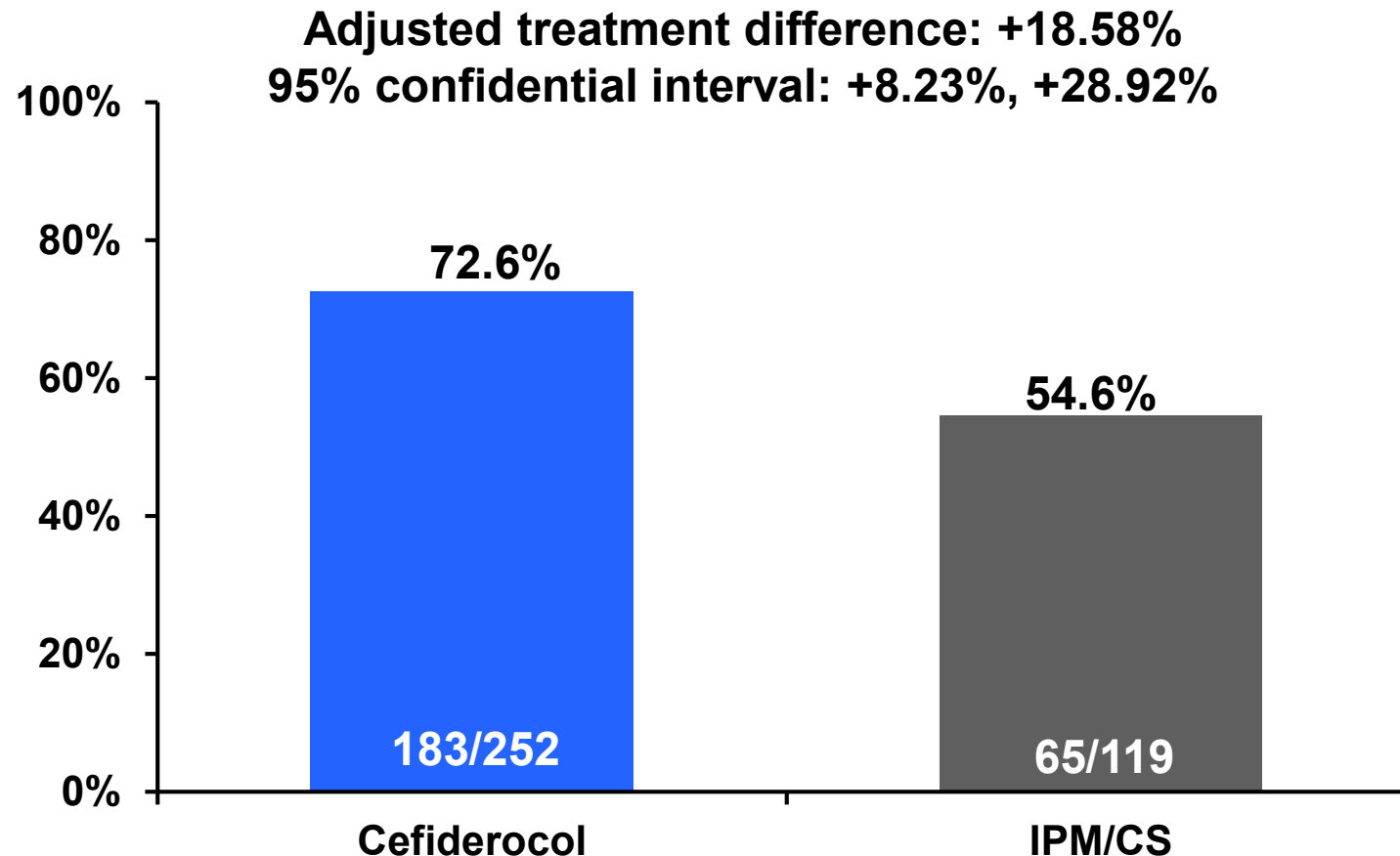


# Treating cUTI Patients Infected with Carbapenem-resistant Pathogens

- Generally not otherwise healthy patients
- Healthcare-associated infections
  - Examples: Post cancer treatment or organ transplant
  - Multiple prior courses of antibiotics
- Typically carbapenem-resistant Enterobacteriaceae and occasionally *Pseudomonas*
- Faced with few options
  - Inactivity of new beta-lactam/beta-lactamase inhibitor combinations if due to metallo beta-lactamases (eg, NDM, VIM, or IMP)
  - **Polymyxins cause kidney injury**
  - **Tetracyclines are bacteriostatic, not used in sepsis or UTI**
- **Patients with MDR pathogens need new effective options without toxicity**

# Review of APEKS-cUTI for Primary Endpoint – Composite Outcome at TOC

- **cUTI: Superior to imipenem (though non-inferiority design)**



# Cefiderocol Risks Seen in cUTI Study

- **Safety consistent with cephalosporin class**
  - No new safety concerns
  - Low rate of *C. difficile* diarrhea
- **Adverse events are unremarkable**
  - <5% diarrhea, hypertension, and constipation; similar to or lower than imipenem
- **Serious adverse events lower than imipenem, generally rare and unrelated to treatment**

# CREDIBLE-CR Study: Possible Reasons for Mortality

- **Safety/toxicology**
  - No pre-clinical concerns
  - No pattern of safety events suggesting toxicity
  - Adjudication committee/DSMB found no evidence of a toxic effect
- **Lack of efficacy**
  - Clinical and microbiology response comparable to BAT
  - Clinical cure 52.5% (42/80) vs 50% (19/38) with BAT
  - Microbiologic persistence 20.0% (16/80) vs 26.3% (10/38) with BAT
- **Chance**
  - Methodological limitations
  - Small descriptive study
  - Multiple infection types

# Review of Mortality in the Other Clinical Trials

- **cUTI Study: Superior to imipenem (though non-inferiority design)**
  - Response rates 72.6% (183/252) vs 54.6% (65/119)
  - 1/300 cefiderocol treated patients died
- **Nosocomial pneumonia: Non-inferiority vs high-dose meropenem**
  - 14-Day mortality 12.4% (18/145) vs 11.6% (17/146)

# Clinicians Need Cefiderocol Today

- **Demonstrated in vitro efficacy against carbapenem-resistant pathogens, regardless of mechanism**
- **The rise of metallo-enzymes and mechanisms of carbapenem resistance other than KPC**
- **Squeezing the balloon with beta-lactam/beta-lactamase inhibitor combinations**
- **The risks of polymyxins in cUTI patients**

# cUTI Benefit/Risk Conclusions

- **Benefits outweigh risks for cUTI**
  - Highly effective for cUTI with superiority to imipenem
  - For patients with cUTI caused by carbapenem-resistant organisms, including NDM metalloenzymes, cefiderocol provides a unique advantage over contemporary antibiotics
  - No renal toxicity
  - Mortality risk in CREDIBLE-CR Study counterbalanced by no mortality risk seen in APEKS-cUTI or APEKS-NP studies

# Experts Available to Address Questions

<b>Bruce Binkowitz, PhD</b>	<b>Statistics Shionogi</b>
<b>Eriko Ogura, MD</b>	<b>Safety Shionogi</b>
<b>Toshihiro Wajima, PhD</b>	<b>Clinical Pharmacology Shionogi</b>
<b>Yoshinori Yamano, PhD</b>	<b>Infectious Disease Pharmacology Shionogi</b>
<b>David Nicolau, PharmD, FCCP, FIDSA</b>	<b>Microbiology Director, Center for Anti-Infective Research and Development Hartford Hospital</b>
<b>Michael Satlin, MD, FIDSA</b>	<b>Infectious Diseases William Randolph Hearst Foundation Clinical Scholar in Microbiology and Infectious Diseases Weill Cornell Medical College</b>
<b>Eric Skaar, PhD, MPH</b>	<b>Microbial Iron Metabolism Professor of Pathology, Microbiology and Immunology Vanderbilt University</b>

# Backup Slides Shown

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# 34 Variables Explored

## CREDIBLE-CR Study

- **Demographics**
  - Sex
  - Age (continuous, categorical)
  - Weight (continuous, categorical)
  - Race
  - CrCl (continuous, categorical)
  - Region
  - Length of hospitalization before randomization
- **Infectious status**
  - Clinical diagnosis
  - APACHE II (continuous, categorical)
  - SOFA (continuous, categorical)
  - Severity by investigator
  - Length of infection before randomization
  - Ventilation at randomization
  - ICU
- **Medical history**
  - Renal replacement therapy
  - Renal disease
  - Severe liver disease
  - Cancer
  - Surgery
  - Cardiac arrest
  - Congestive heart failure
  - Dementia and Parkinson's
  - COPD
  - Acute Respiratory Distress Syndrome
  - Diabetes
  - Past vasopressor use
  - Charlson comorbidity index (continuous, categorical)
  - Metastatic solid tumor
  - Diabetes and chronic complications
- **Medical history (within 31 days before randomization)**
  - Cerebrovascular disease
  - Shock
  - Myocardial infarction
  - Surgery
  - Trauma

# Logistic Regression Model for in-Study 49-Day Mortality (1 of 3)

## CREDIBLE-CR Study (Safety Population)

Covariate	Adjusted Odds Ratio for Treatment [95% CI]	Unadjusted Odds Ratio for Treatment [95% CI]	Percent Change of Log OR
Age (≥65 or <65)	1.76 [0.77, 4.02]	1.98 [0.88, 4.44]	-16.8%
Ventilation	2.21 [0.95, 5.13]	1.98 [0.88, 4.44]	15.9%
Trauma	2.20 [0.97, 4.99]	1.98 [0.88, 4.44]	15.6%
Charlson Comorbidity Index (≥6, ≤5)	2.20 [0.94, 5.12]	1.98 [0.88, 4.44]	15.2%
SOFA (Continuous)	2.21 [0.93, 5.26]	2.01 [0.90, 4.51]	13.6%
Congestive heart failure	2.15 [0.94, 4.91]	1.98 [0.88, 4.44]	12.0%
Renal replacement therapy	1.83 [0.81, 4.14]	1.98 [0.88, 4.44]	-11.7%
Myocardial infarction	1.83 [0.81, 4.12]	1.98 [0.88, 4.44]	-11.7%
ICU	1.84 [0.81, 4.17]	1.98 [0.88, 4.44]	-10.5%
Shock within 31 days of randomization	1.85 [0.79, 4.32]	1.98 [0.88, 4.44]	-10.2%
CrCL (<50, or ≥50)	1.86 [0.82, 4.20]	1.98 [0.88, 4.44]	-9.4%
Charlson Comorbidity Index (Continuous)	2.11 [0.89, 5.00]	1.98 [0.88, 4.44]	9.1%
Renal disease	2.10 [0.91, 4.85]	1.98 [0.88, 4.44]	8.9%
Clinical diagnosis	2.10 [0.93, 4.77]	1.98 [0.88, 4.44]	8.8%
Past vasopressor use	2.08 [0.91, 4.78]	1.98 [0.88, 4.44]	7.6%
Surgery or Trauma	2.08 [0.92, 4.71]	1.98 [0.88, 4.44]	7.4%

# Comparison of the Demographic, Clinical, and Microbiological Parameters Between the CREDIBLE-CR Pneumonia and APEKS-NP Study Populations (ITT Populations)

Variable		CREDIBLE-CR, HAP/VAP/HCAP N=67	APEKS-NP N=298
Diagnosis	HAP, %	40.3	40.6
	VAP, %	55.2	41.9
	HCAP, %	4.5	17.4
Ventilated	Yes %	74.6	59.7
Age	Mean	63.9	65.2
Gender	Male, %	76.1	68.8
CrCL	<50 mL/min, %	32.8	33.9
APACHE II	Score > 16, %	56.7	48.7
	Mean score	17.1	16.2
Treatment failure, %		64.2	32.6
Baseline pathogen, %	<i>A. baumannii</i>	55.2	15.8
	<i>K. pneumoniae</i>	25.4	30.9
	<i>P. aeruginosa</i>	25.4	16.1
	<i>E. coli</i>	7.5	13.8
	<i>S. maltophilia</i>	7.5	1.3

# Microbiological Response

## cUTI Study

- **Eradication:** A urine culture shows the bacterial uropathogen(s) found at baseline at  $\geq 10^5$  CFU/mL are reduced to  $< 10^4$  CFU/mL
- **Persistence:** A urine culture shows that the original bacterial uropathogen(s) found at entry at  $\geq 10^5$  CFU/mL grows  $\geq 10^4$  CFU/mL
- **Indeterminate:** No urine culture collected/outside protocol window/lost to follow up

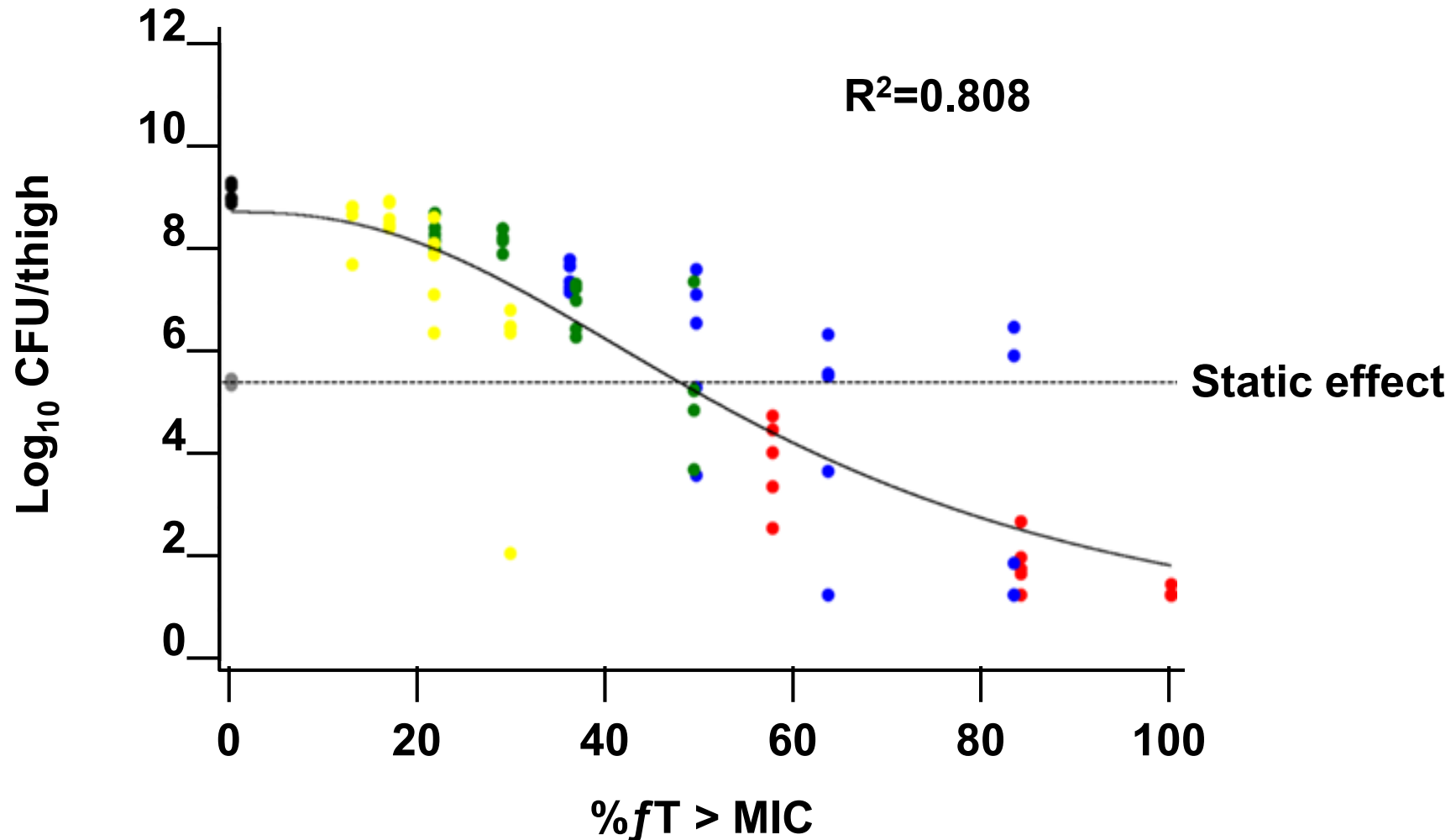
# Patients with Bacteremia at Baseline

## cUTI Study (Micro-ITT Population)

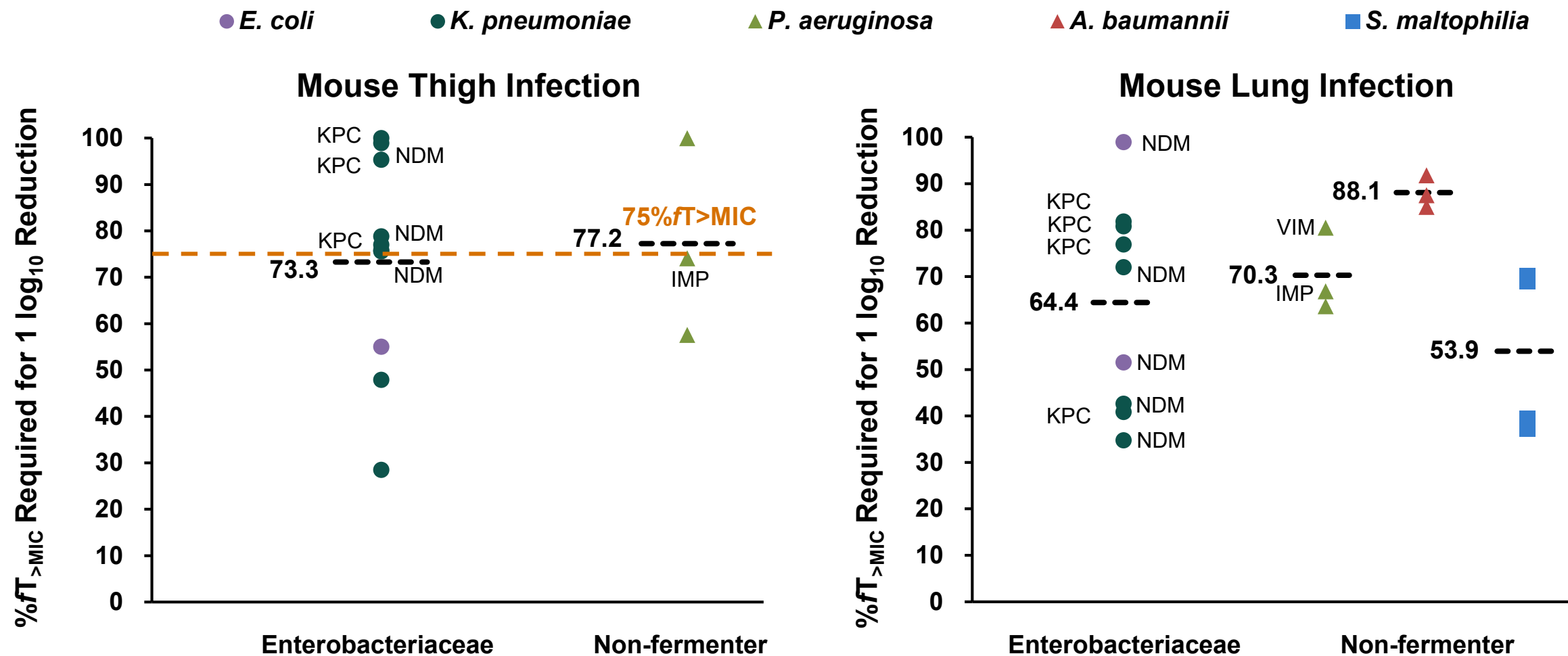
Outcome	Cefiderocol N=18 n (%)	Imipenem/Cilastatin N=8 n (%)
Postbaseline Blood Culture*		
Negative	15 (83.3)	6 (75.0)
No data	3 (16.7)	0 (0.0)
Positive	0 (0.0)	2 (25.0)
Clinical Outcome at TOC		
Clinical Cure	14 (77.8)	5 (62.5)
Indeterminate	3 (16.7)	1 (12.5)
Clinical Failure	1 (5.6)	2 (25.0)
Microbiological Outcome (Urine) at TOC		
Eradication	10 (55.6)	3 (37.5)
Indeterminate	6 (33.3)	4 (50.0)
Persistence	2 (11.1)	1 (12.5)

\* Negative at least once postdose.

# Correlation of %fT>MIC with Efficacy in Neutropenic Mouse Thigh Infection Model Caused by *P. aeruginosa*



# Target % $fT >_{MIC}$ of Cefiderocol Required for 1-log Reduction in Mouse Thigh and Lung Infection Models



# AEs Related to Anemia in Clinical Trials

## Safety Population

cUTI Study	Cefiderocol N=300	Imipenem N=148
PT	%	%
AEs related to anemia (total)	1.0	0.7
Anemia	0.3	0.7
Iron deficiency anemia	0.3	0
Hemorrhagic anemia	0.3	0
CREDIBLE-CR Study	Cefiderocol N=101	BAT N=49
PT	%	%
AEs related to anemia (total)	9.9	6.1
Anemia	7.9	4.1
Anemia of chronic disease	1.0	2.0
Normochromic normocytic anemia	1.0	0

# Anemia-related TEAEs

## APEKS-NP Study (Safety Population)

System Organ Class Preferred Term	Cefiderocol N=148 n (%)	Meropenem N=150 n (%)
Blood and lymphatic system disorders	27 (18.2)	28 (18.7)
Anemia	12 (8.1)	12 (8.0)
Anemia of chronic disease	2 (1.4)	0
Hemorrhagic anemia	0	2 (1.3)
Iron deficiency anaemia	3 (2.0)	0
Nephrogenic anaemia	0	1 (0.7)
Normochromic normocytic anaemia	1 (0.7)	0
Investigations	32 (21.6)	29 (19.3)
Hemoglobin decreased	1 (0.7)	0
Red blood cell count decreased	1 (0.7)	0

# All-cause Mortality Rate by Concomitant Therapy

## Blood Transfusion and Iron Preparation

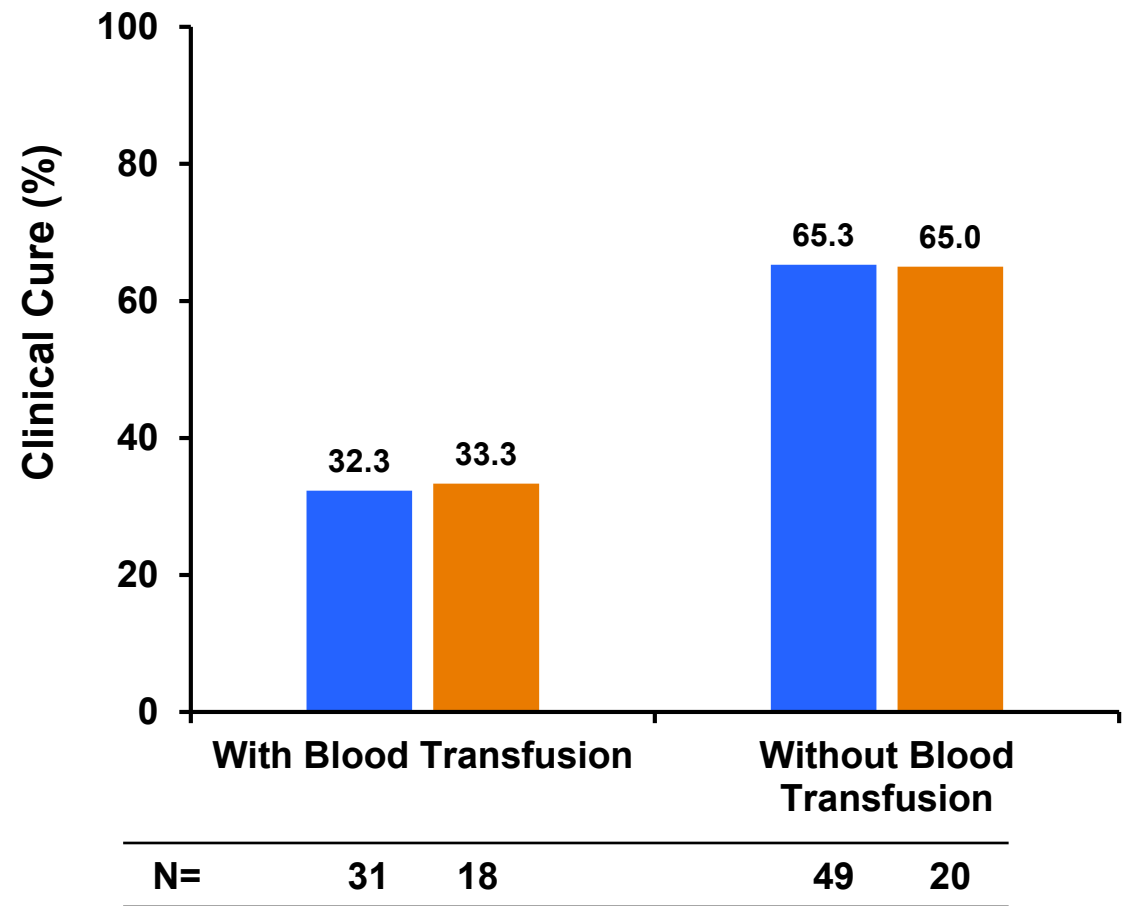
All-cause Mortality Subgroup	Cefiderocol N=101 n/N' (%)	BAT N=49 n/N' (%)
Blood transfusion		
Yes	18/37 (48.6)	6/21 (28.6)
No	6/64 (25.0)	3/28 (10.7)
Iron preparation		
Yes	3/11 (27.3)	1/7 (14.3)
No	31/90 (34.4)	8/42 (19.0)

# Summary of Clinical and Microbiological Outcome by Blood Transfusion

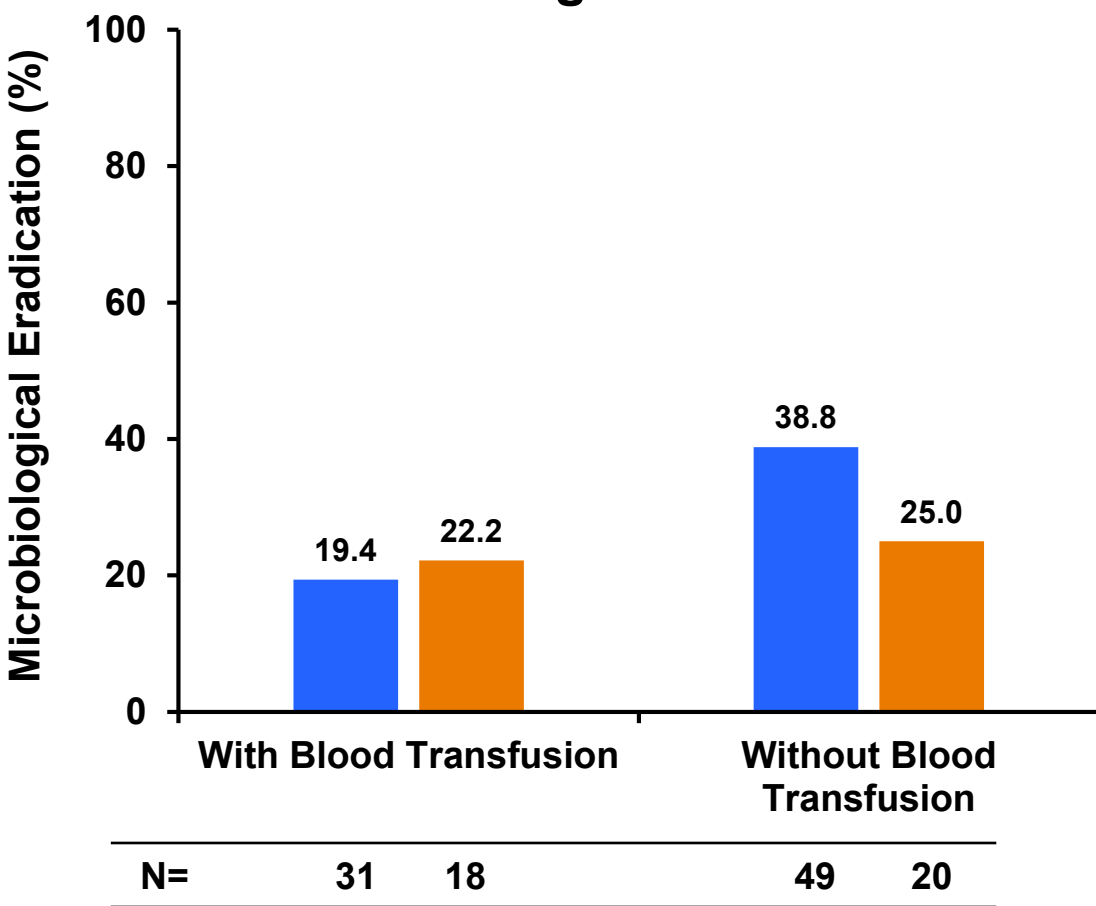
Carbapenem-resistant Microbiological ITT Population (N=118)

Cefiderocol BAT

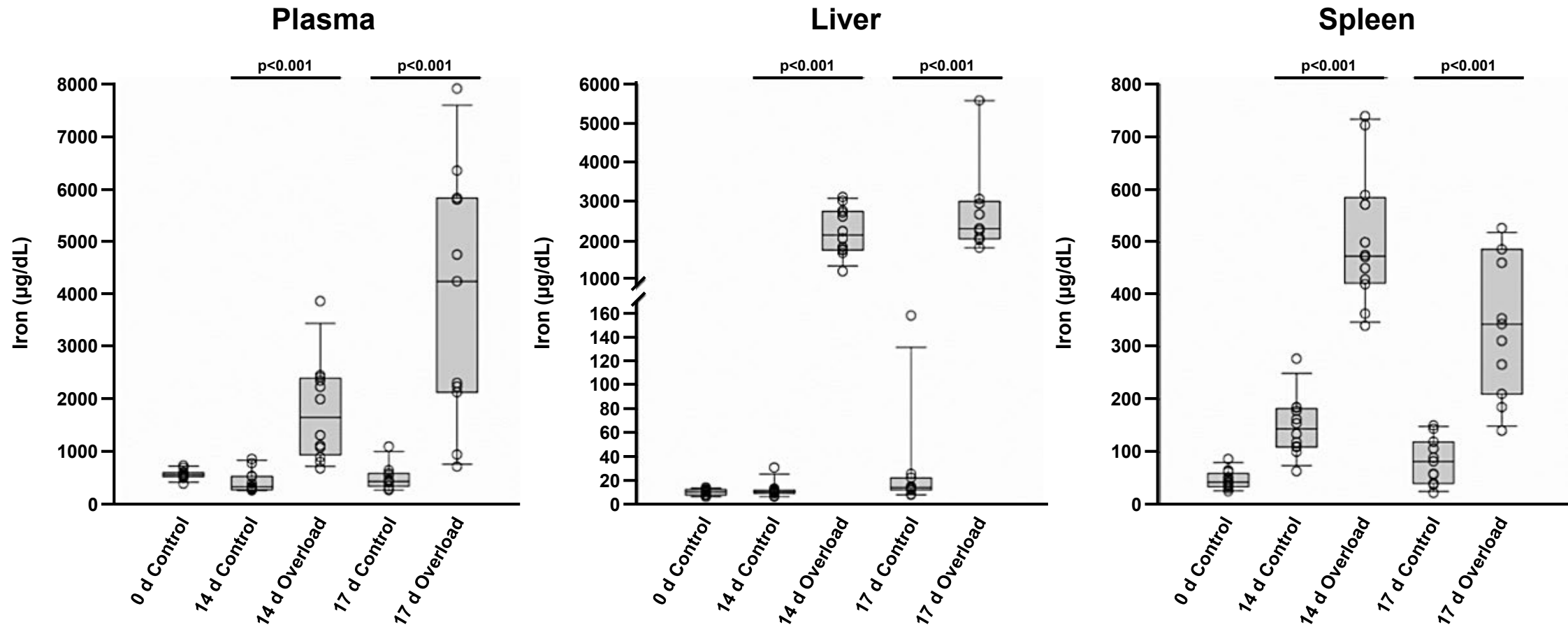
Clinical Cure



Microbiological Eradication



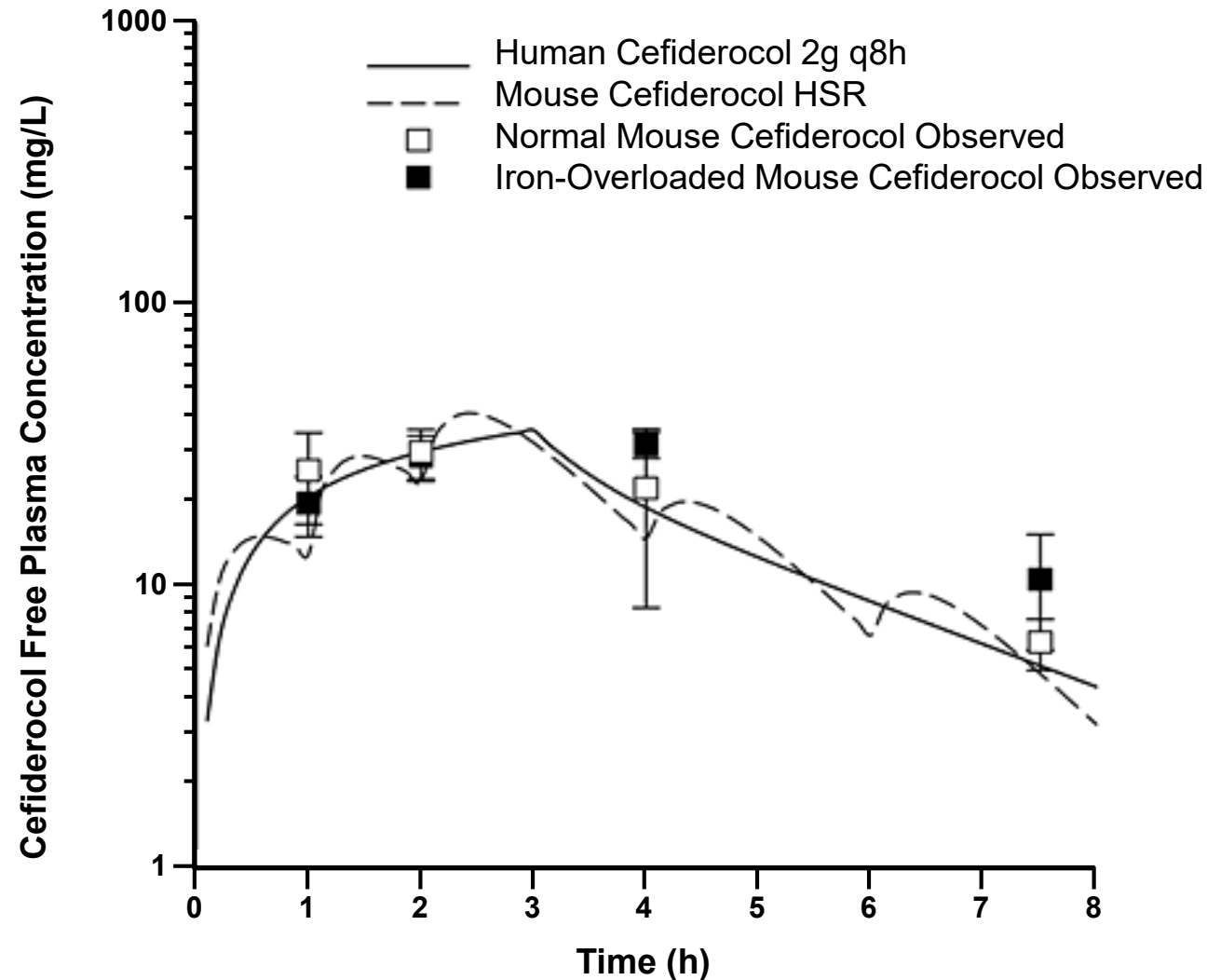
# Iron Concentrations in Plasma, Liver, and Spleen Tissue for Iron-Overloaded Mice



Open circles represent iron concentrations; horizontal lines within boxes represent median values; while box lower and upper borders represent 1st and 3rd quartiles; whiskers represent 10th and 90th percentiles.

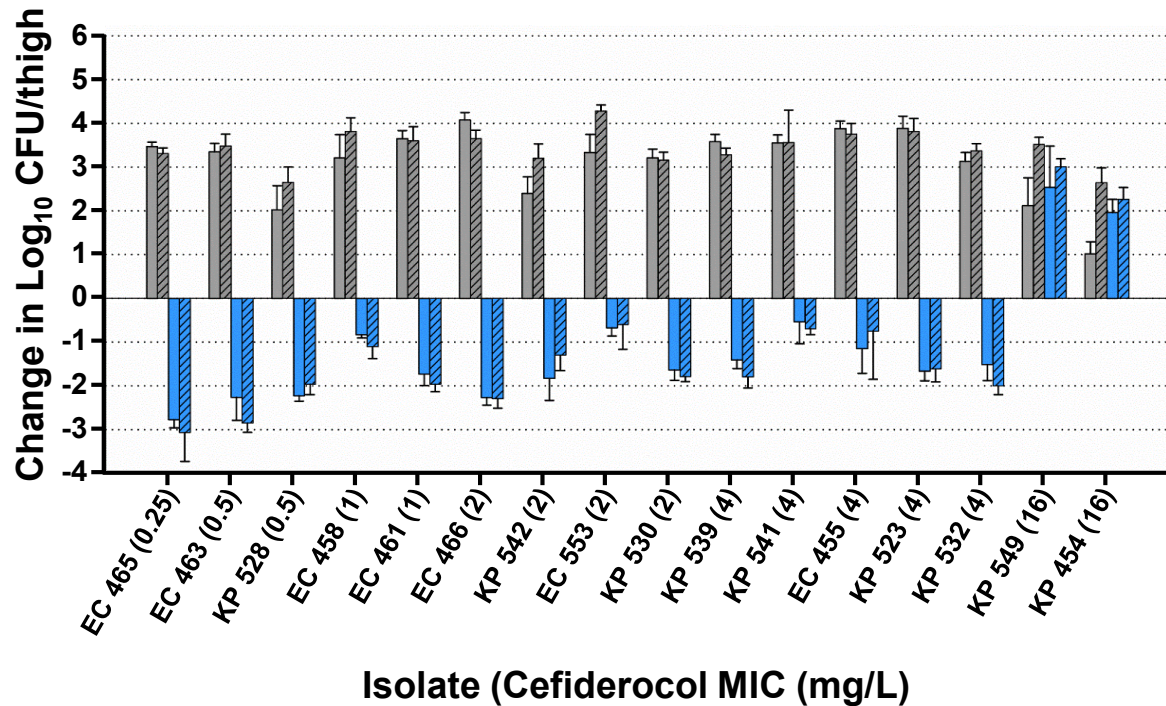
p<0.001: significant difference (median iron content per treatment group was compared to same age controls using the nonparametric Mann-Whitney rank sum test.)

# PK of Cefiderocol in Plasma of the Thigh Infection Models Under Humanized PK Exposure Using Iron-Overloaded Mice

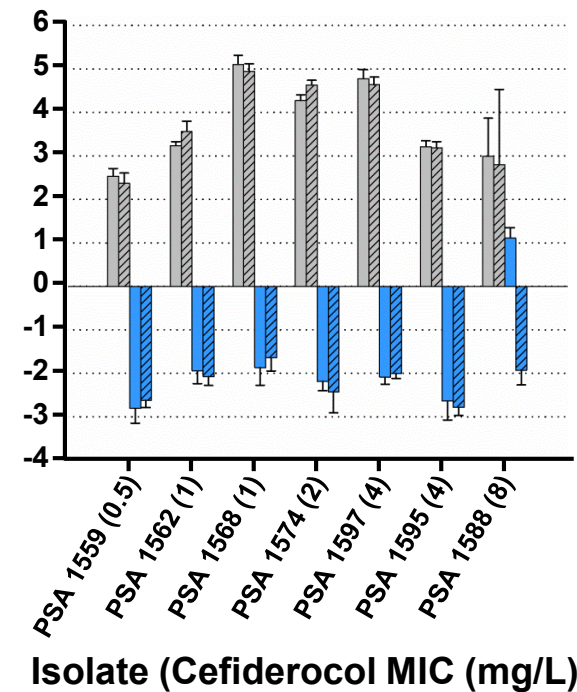


# Efficacy in the Thigh Infection Models Under Humanized PK Exposure Using Iron-Overloaded Mice

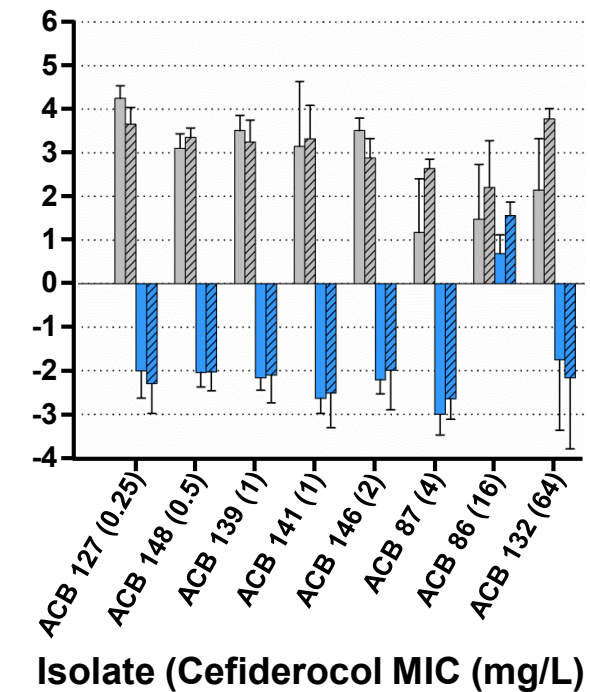
Enterobacteriaceae



*P. aeruginosa*



*A. baumannii*



Saline, Normal Model    Saline, Iron Overload Model    Cefiderocol HSR, Normal Model    Cefiderocol HSR, Iron Overload Model

# Monitoring for Resistance/Changes in MIC

## cUTI Study (Micro-ITT Population)

	Cefiderocol N = 252	IPM/CS N = 119
Number of patients with ≥ 4-fold increase from Baseline in MIC for the Study Treatment	6*	3***
Highest MIC	1 µg/mL**	>8 µg/mL

- \* One additional patient in the cefiderocol group with *Pseudomonas* cleared infection at TOC but had a new *Pseudomonas* isolate with MIC of 8 µg/mL at FU, confirmed by electrophoresis to be different from baseline organism
- \*\* Excluding the patient with new isolate of *Pseudomonas* with MIC 8 µg/mL
- \*\*\* Only 1 of these patients developed IPM resistance (*P. aeruginosa* MIC increased from 1 to >8 µg/mL at TOC and FU)  
One additional patient (with *P. mirabilis*, not in table) developed resistance with 2-fold change in MIC (from 2 [intermediate] to 4 µg/mL [resistant])

# Monitoring for Resistance/Changes in MIC

## CREDIBLE-CR Study (CR Micro-ITT Population)

	Cefiderocol N=80	BAT N=38
Number of patients with $\geq 4$ -fold increase from Baseline in MIC for the study treatment	15 (19%)	5 (13%)
Number of patients with MIC $\geq 8$ for cefiderocol, or MIC above breakpoint for BAT	4 (5%) <sup>a</sup>	5 (13%) <sup>b</sup>

a. Cefiderocol (4 patients, 4 pathogens)

- 3 *A. baumannii*: cefiderocol (8) , cefiderocol (8), cefiderocol ( $>64$ )
- 1 *P. aeruginosa*: cefiderocol (16)

b. BAT (5 patients, 6 pathogens)

- 3 *K. pneumoniae*: ceftazidime/avibactam (16), colistin ( $>8$ ), tigecycline ( $>4$ ) / colistin (8)
- 2 *A. baumannii*: tigecycline ( $>4$ ) / colistin ( $>8$ ), colistin ( $>8$ )
- 1 *E. coli*: colistin (8)

# Monitoring for Resistance/Changes in MIC

## APEKS-NP Study (Modified-ITT Population)

	Cefiderocol N=145	Meropenem N=147
Number of patients with $\geq 4$ -fold increase from Baseline in MIC for the Study Treatment	9 (6.2%)	9 (6.1%)
Number of patients with MIC $\geq 8$ for cefiderocol, or MIC $\geq 16$ for meropenem	1 <sup>a</sup> (0.7%)	5 <sup>b</sup> (3.4%)

- a. Cefiderocol
  - *K. pneumoniae* (8)
- b. Meropenem
  - 4 *A. baumannii*: meropenem (64), meropenem (64), meropenem (>64), meropenem (>64)
  - 1 *P. aeruginosa*: meropenem (64)

# Patients With $\geq 4$ -fold Change in MIC to Cefiderocol

## cUTI Study (Micro-ITT Population)

- Six out of 252 patients in the cefiderocol group showed  $\geq 4$ -fold change in MIC for cefiderocol in the baseline pathogen during the study
- No MIC was higher than 1  $\mu\text{g/mL}$
- One additional patient with *Pseudomonas* cleared infection at TOC but had a new isolate at FU that was a genetically different organism (MIC 8  $\mu\text{g/mL}$ )

Subject	Visit	Gram-negative Uropathogen	MIC to Cefiderocol ( $\mu\text{g/mL}$ )
#1	Baseline	<i>E. coli</i>	0.03
	Follow-up		0.25*
#2	Baseline	<i>E. cloacae complex</i>	0.12
	Test of Cure		0.5*
	Follow-up		0.25
#3	Baseline	<i>E. coli</i>	0.25
	Test of Cure		0.5
	Follow-up		1*
#4	Baseline	<i>E. coli</i>	0.03
	Test of Cure		0.12*
	Follow-up		0.06
#5	Baseline	<i>P. mirabilis</i>	0.06
	Test of Cure		0.5*
	Follow-up		0.03
#6	Baseline	<i>E. aerogenes</i>	0.015
	Follow-up		0.12*

\* Indicates  $\geq 4$ -fold increase in MIC from Baseline; MIC = minimum inhibitory concentration.

# Increase of MIC of $\geq 4$ fold During Cefiderocol and BAT Treatment

## CREDIBLE-CR (CR Micro-ITT Population)

Cefiderocol			
Isolates	MIC (mg/mL)		MIC Increase
	Pre	Post	
<i>A. baumannii</i>	0.25	1	4
	1	8	8
	1	4	4
	2	>64	>32
	0.25	4	16
	1	8	8
	0.06	1	16
<i>K. pneumoniae</i>	0.25	2	8
	0.12	0.5	4
	0.06	0.5	8
	$\leq 0.03$	2	>64
<i>P. aeruginosa</i>	0.25	2	8
	0.5	2	4
	0.12	16	128
<i>S. maltophilia</i>	0.06	0.25	4
	0.06	0.25	4

BAT				
Treatment	Isolates	MIC (mg/mL)		MIC Increase
		Pre	Post	
Ceftazidime/ avibactam	<i>K. pneumoniae</i>	0.25	16	64
	<i>K. pneumoniae</i>	1	>4	>4
Tigecycline	<i>A. baumannii</i>	2	>4	>2
	<i>K. pneumoniae</i>	$\leq 0.5$	>8	>16
Colistin	<i>K. pneumoniae</i>	$\leq 0.5$	8	>16
	<i>E. coli</i>	2	8	4
	<i>A. baumannii</i>	1	>8	>8
	<i>A. baumannii</i>	$\leq 0.5$	>8	>16

# Outcomes in Patients with ≥4-fold Change in MIC to Cefiderocol

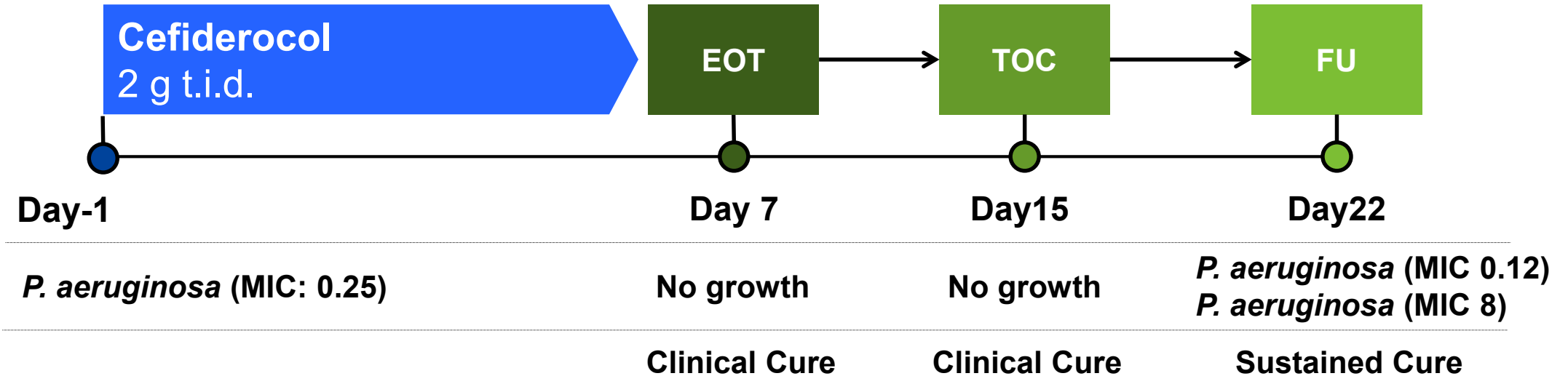
## cUTI Study (Micro-ITT Population)

Patient	Visit	Gram-negative Uropathogen	MIC to Cefiderocol (µg/mL)	Composite Outcome at TOC / FU
#1	Baseline	<i>E. coli</i>	0.03	Response / Failure
	Follow-up		0.25*	
#2	Baseline	<i>E. cloacae complex</i>	0.12	Failure / Failure
	Test of Cure Follow-up		0.5* 0.25	
#3	Baseline	<i>E. coli</i>	0.25	Response / Response**
	Test of Cure Follow-up		0.5 1*	
#4	Baseline	<i>E. coli</i>	0.03	Failure / Failure
	Test of Cure Follow-up		0.12* 0.06	
#5	Baseline	<i>P. mirabilis</i>	0.06	Failure / Failure
	Test of Cure Follow-up		0.5* 0.03	
#6	Baseline	<i>E. aerogenes</i>	0.015	Response / Failure
	Follow-up		0.12*	

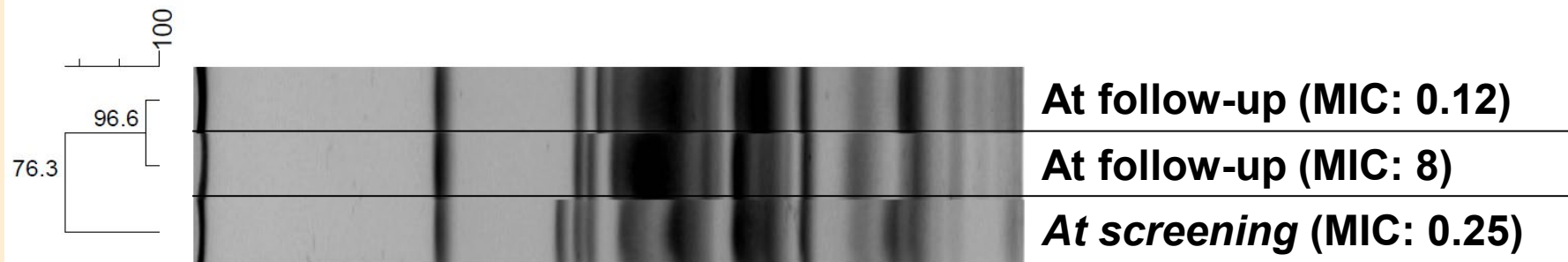
\* Indicates ≥4-fold change in MIC to cefiderocol  
\*\* This subject had recurrence at a second FU visit 2weeks later

# New Isolate of *P. aeruginosa* with MIC 8 µg/mL

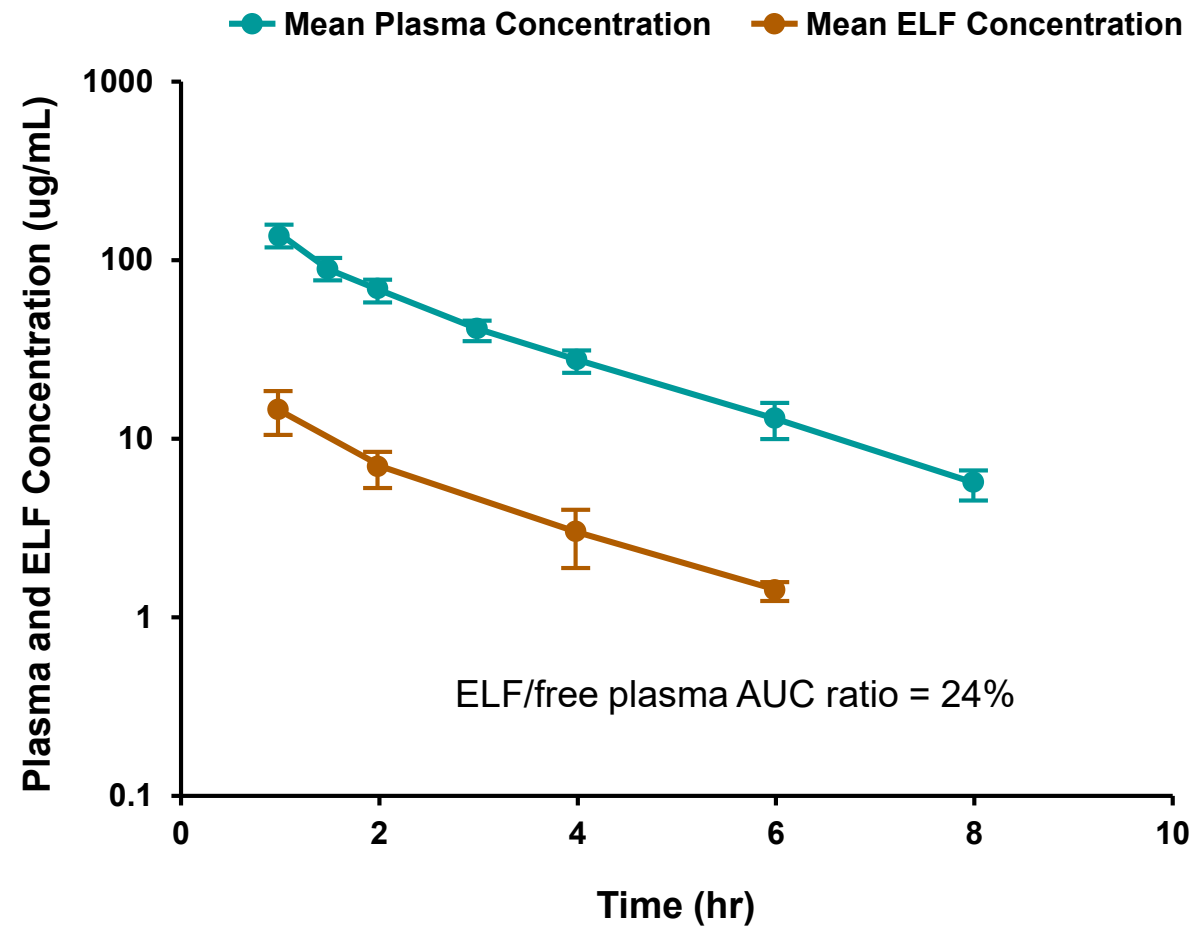
## cUTI Study



### PFGE Result



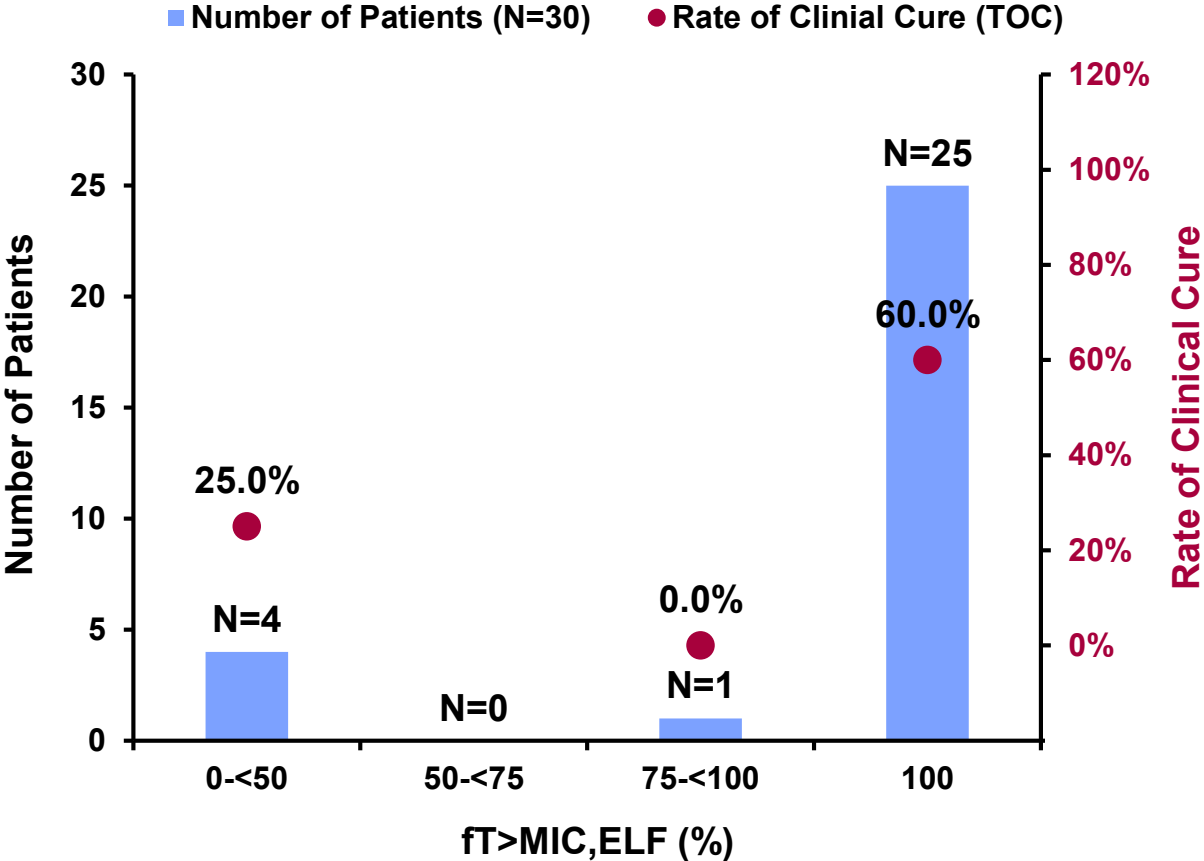
# Plasma and ELF Concentration Profiles in Healthy Subjects



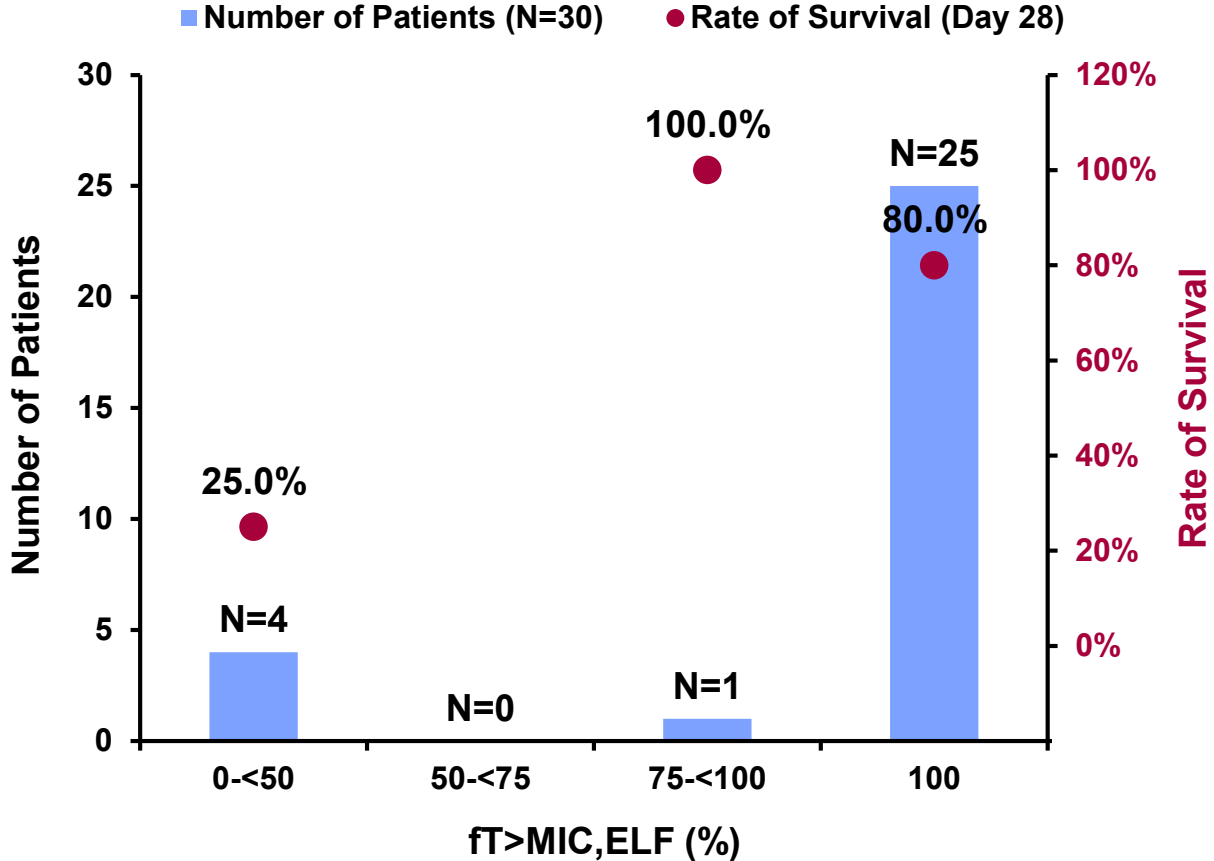
# Relationships Between ELF %fT>MIC and Outcomes

## CREDIBLE-CR Study

Clinical Cure at TOC for Pneumonia  
(N=30)



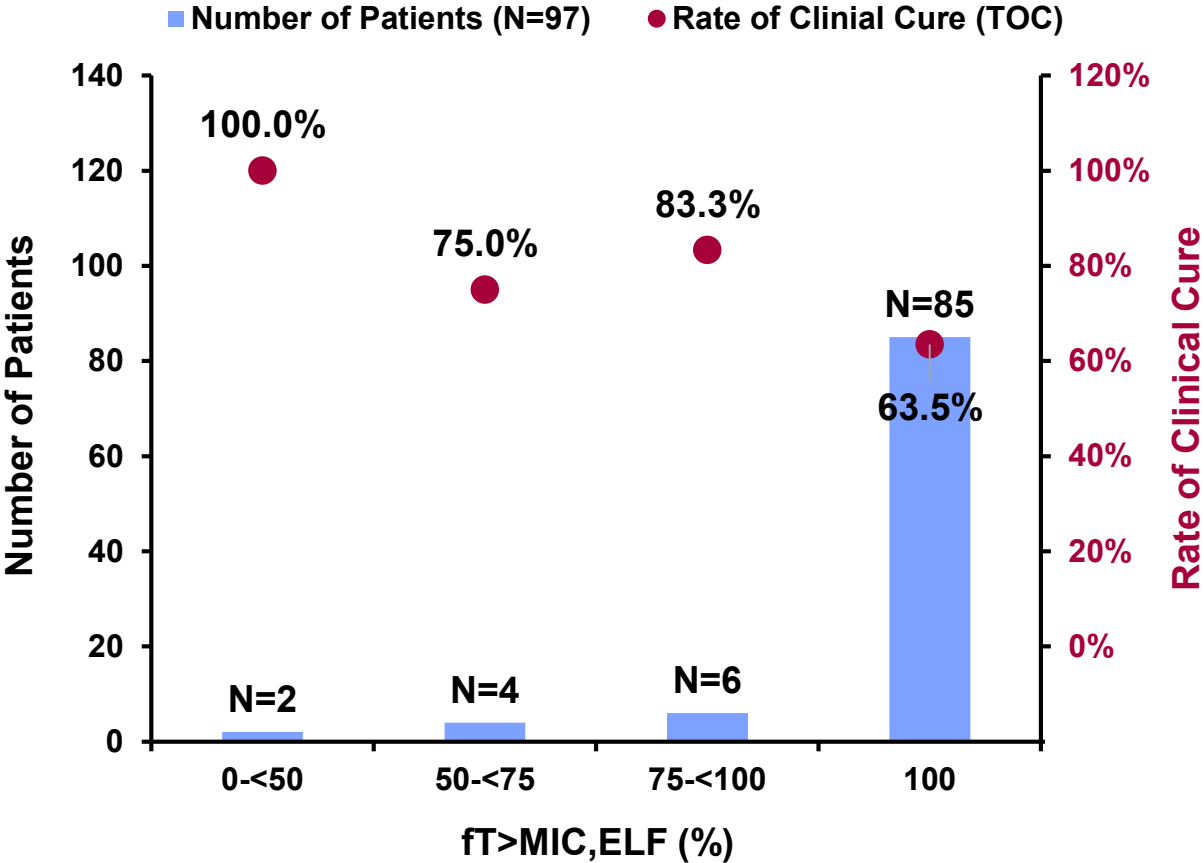
Survival on Day 28 for Pneumonia  
(N=30)



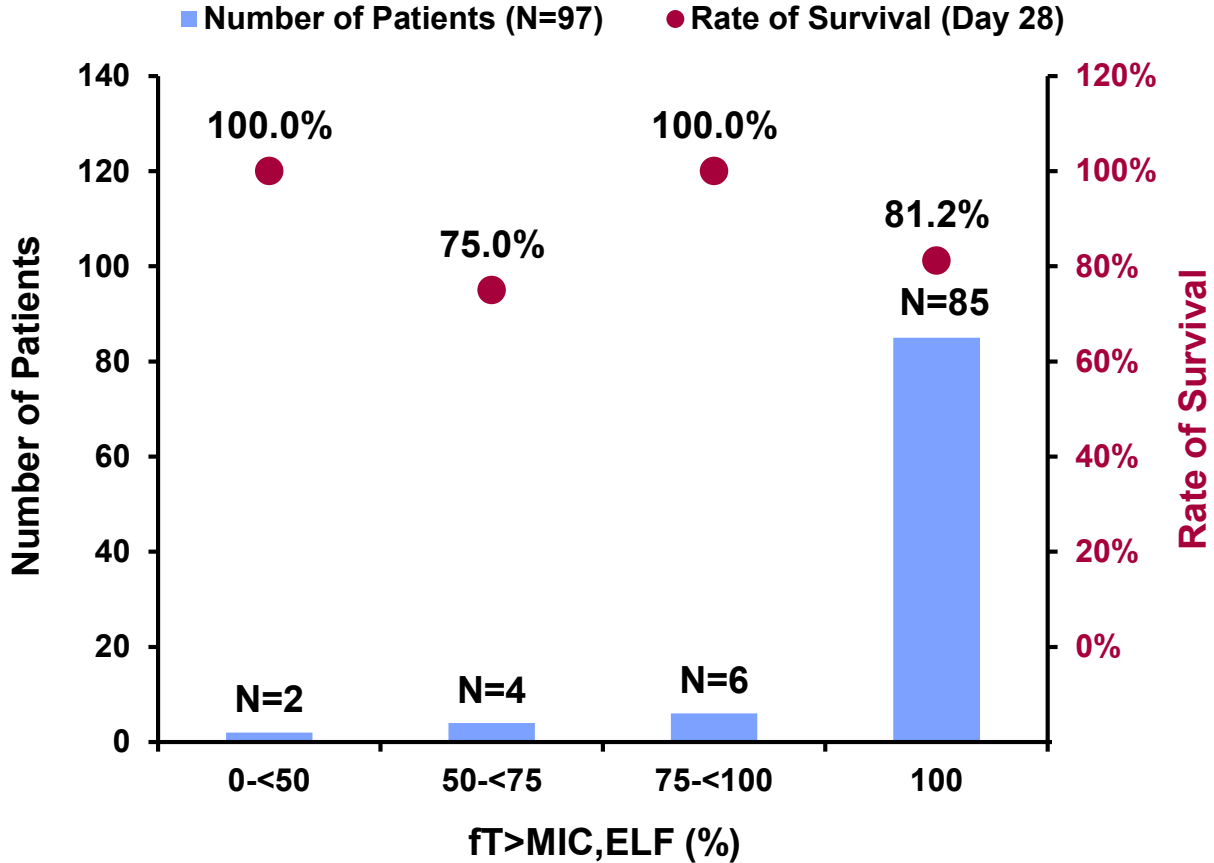
# Relationships Between ELF %fT>MIC and Outcomes

## APEKS-NP Study

Clinical Cure at TOC for Pneumonia  
(N=97)

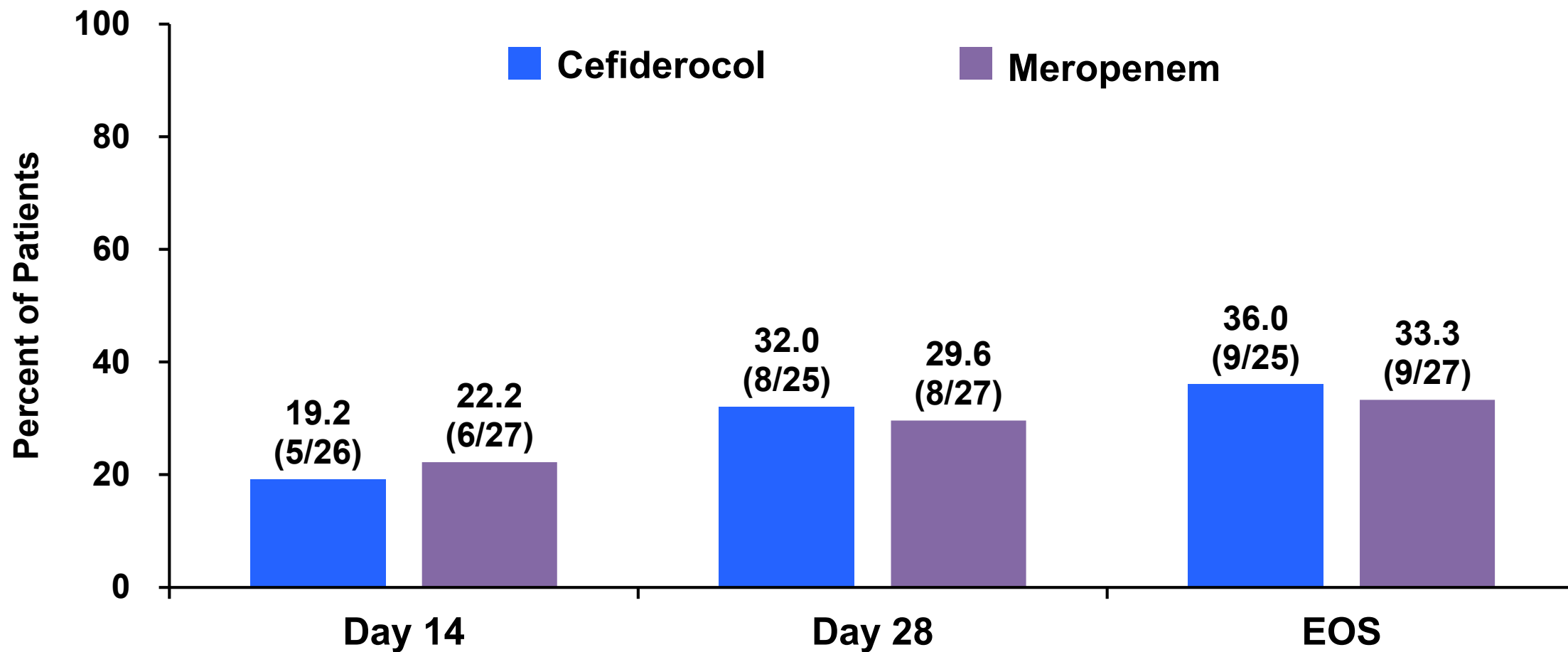


Survival on Day 28 for Pneumonia  
(N=97)



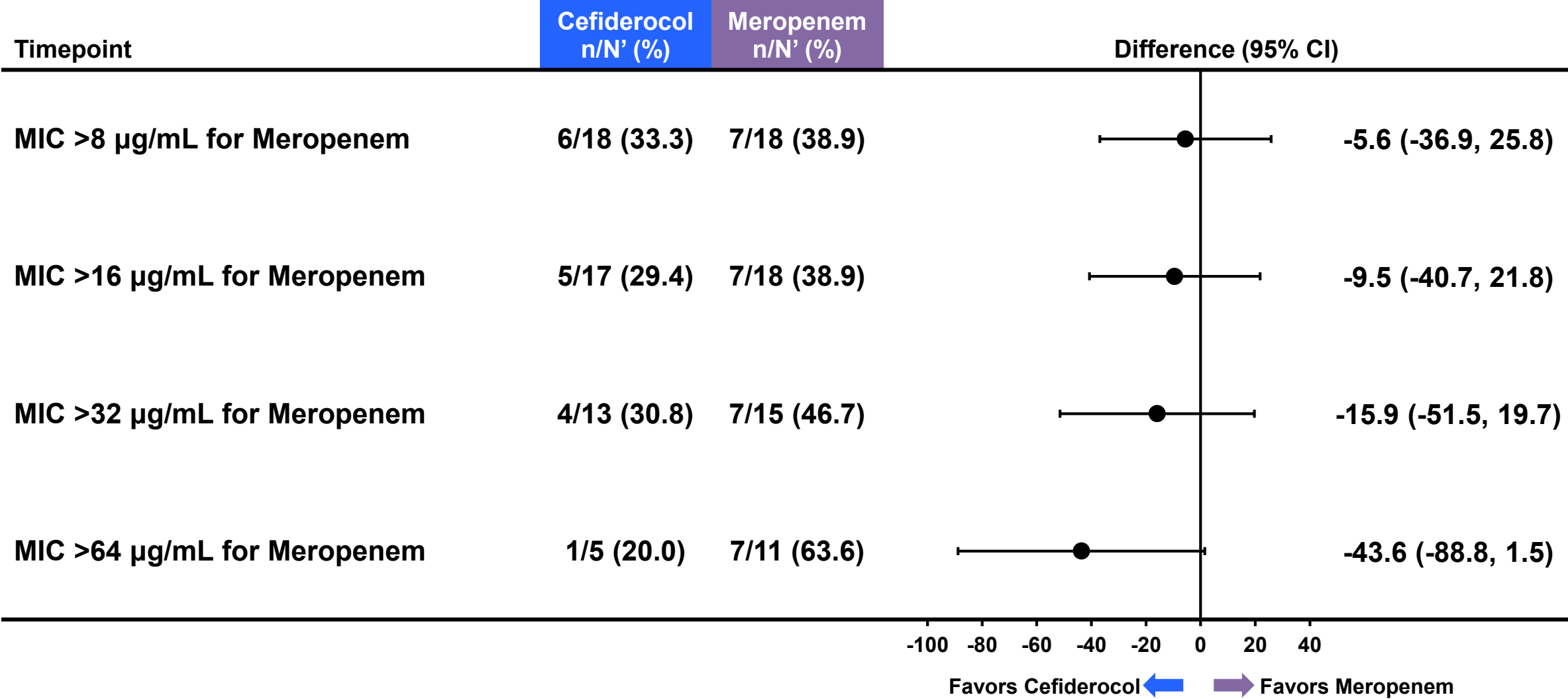
# All-cause Mortality for Patients with *Acinetobacter* spp.

## APEKS-NP Study (Modified-ITT Population)



# Comparison of ACM at Day 28 by MIC Values *Acinetobacter* spp.

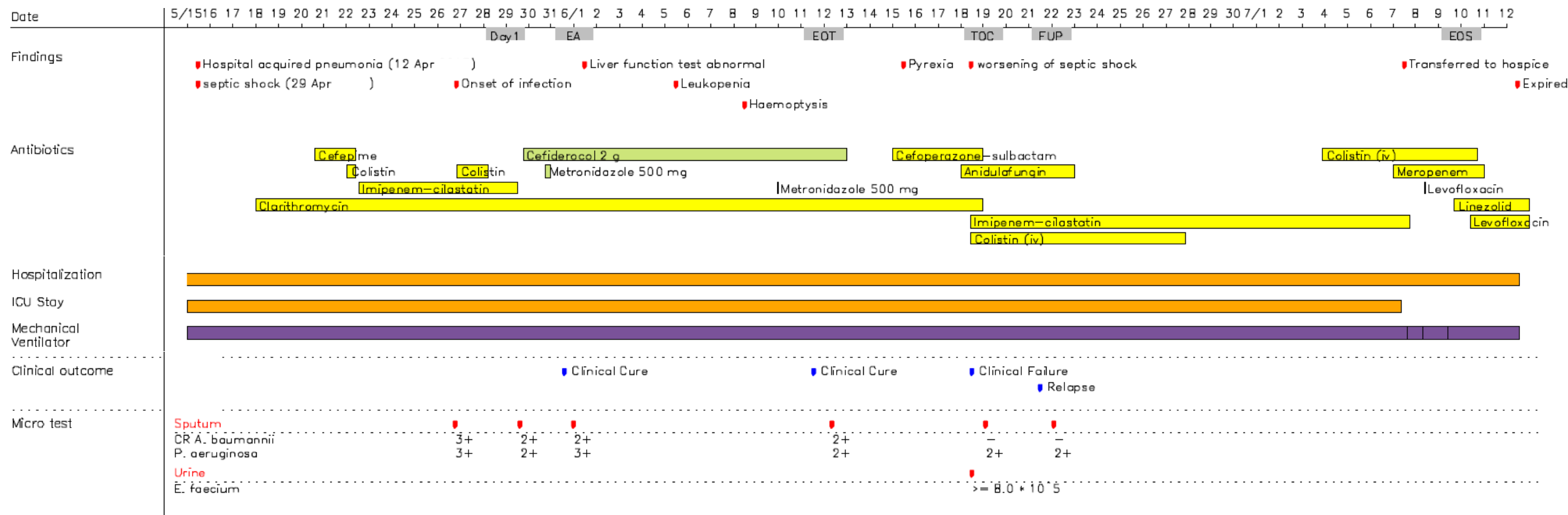
APEKS-NP Study (Modified-ITT Population)



Patients with MIC of ≥4 Fold Increase on Cefiderocol Treatment  
Who Died (2/2)  
CREDIBLE-CR Study (Safety Population)

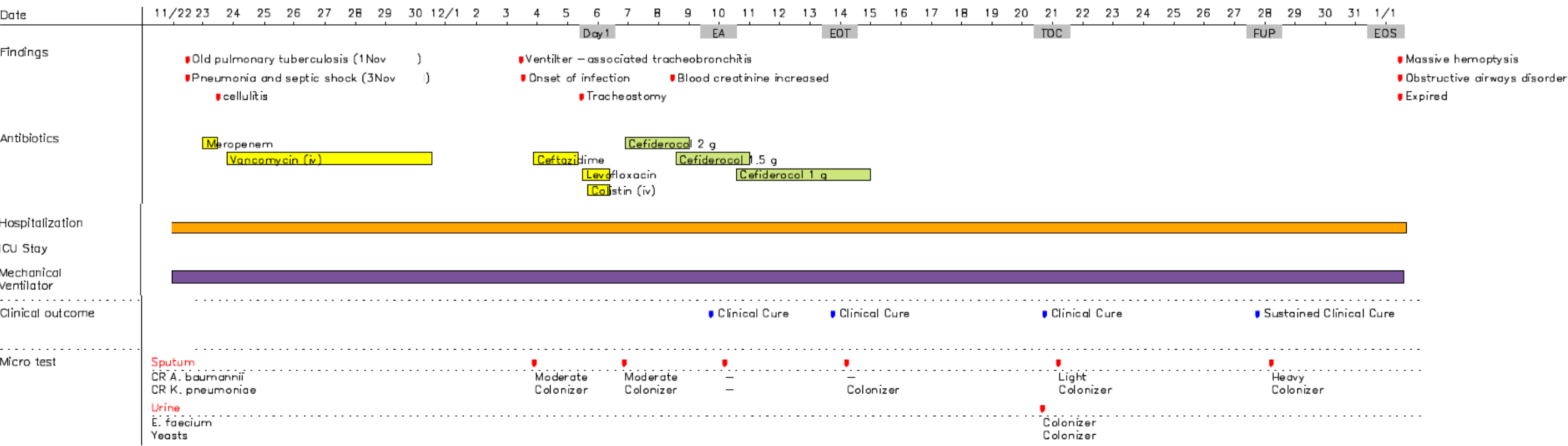
Diagnosis	Pathogen	MIC (Baseline/ Increased)	Comorbidity	ICU/ Shock	Clinical/Micro Outcome at TOC	Cause of Death/ Notes
HAP	<i>K. pneumoniae</i> <i>A. baumannii</i> <i>E. coli</i>	0.25/2	Ruptured AAA, ischemic bowel	Y/N	Failure/ Persistence	Septic shock/ Perforated bowel
VAP	<i>S. maltophilia</i> <i>A. nosocomialis</i> <i>C. indologenes</i> <i>P. aeruginosa</i>	0.06/0.25	Hepatic cirrhosis SBP, bleeding varices	Y/Y	Indeterminate/ Indeterminate	Hepatitis, Sepsis
VAP	<i>A. baumannii</i> <i>P. aeruginosa</i>	1/8	Cirrhosis, respiratory failure, AKI	Y/Y	Failure/ Persistence	Septic shock
Sepsis	<i>A. baumannii</i>	2/>64	Gangrenous cholecystitis	N/N	Cure/ Persistence	Obstructive airways disorder

# Patient #8 (FDA Patient #15): VAP Due to *CR A. baumannii*, *P. aeruginosa* Bronchiectasis, Hepatic Cirrhosis, Lymphoma



CR <i>A. baumannii</i>				<i>P. aeruginosa</i>			
CFDC	1	CFPM	>16	CFDC	0.12	CFPM	16
IPM	16	CPFX	>4	IPM	0.5	CPFX	2
MEPM	32	CAZ/AVI	2	MEPM	0.25	CAZ/AVI	2
CST	1	CEF/TAZ	16	CST	2	CEF/TAZ	1
AMK	>64	TGC	>4	AMK	<=4	TGC	>4
AZT	16			AZT	8		

# Patient #10 (FDA Patient #34): Sepsis Due to CR *A. baumannii*, CR *K. pneumoniae*, Acute Kidney, Cholecystitis Infective, COPD



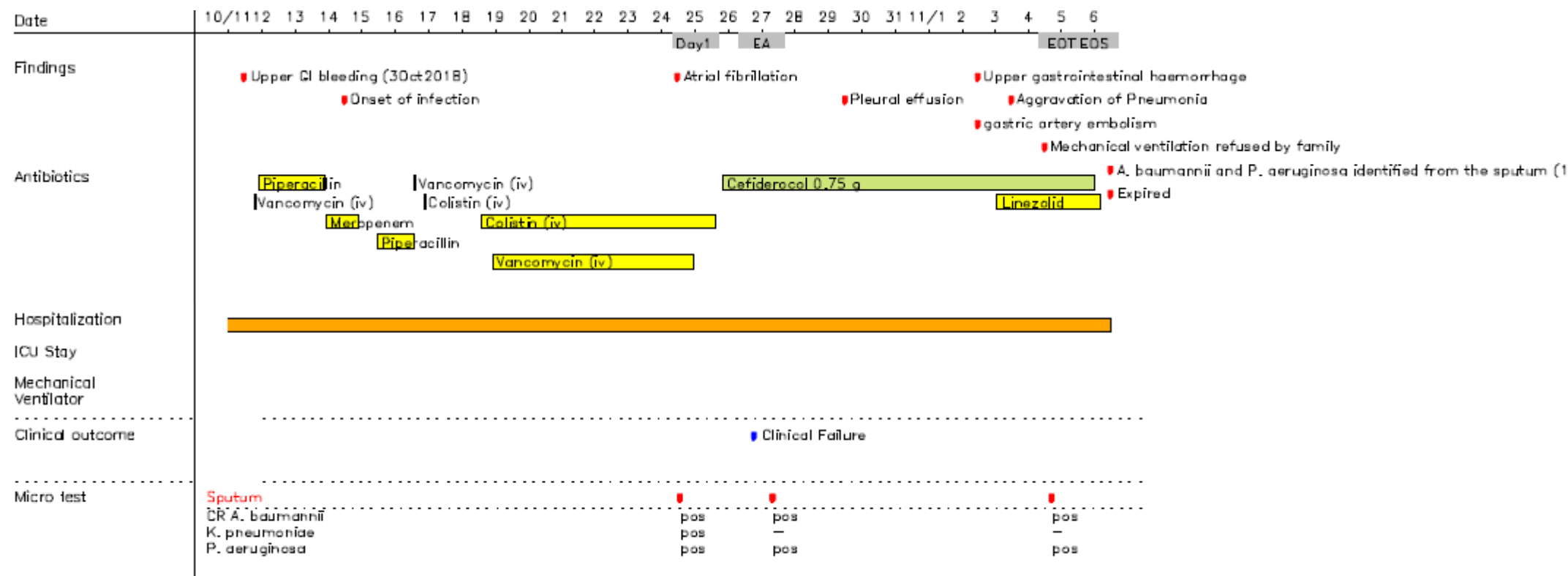
CR <i>A. baumannii</i>			
CFDC	:2	CFPM	>16
IPM	:64	CPFX	>4
MEPM	>64	CAZ/AVI	>64
CST	:1	CEF/TAZ	>64
AMK	>64	TGC	:0.5
AZT	>32		

CR <i>K. pneumoniae</i>			
CFDC	:2	CFPM	>16
IPM	:32	CPFX	>4
MEPM	:32	CAZ/AVI	:1
CST	:1	CEF/TAZ	>64
AMK	:≤4	TGC	:0.5
AZT	>32		

Patients with MIC of  $\geq 4$  Fold Increase on Cefiderocol Treatment  
Who Died (1/2)  
CREDIBLE-CR Study (Safety Population)

Diagnosis	Pathogen	MIC (Baseline/ Increased)	Comorbidity	ICU/ Shock	Clinical/Micro Outcome at TOC	Cause of Death/ Notes
VAP	<i>A. baumannii</i>	0.25/1	Pulmonary hemorrhage	Y/Y	Failure/ Indeterminate	Sepsis/ <i>C. tropicalis</i> candidemia MOF
VAP	<i>A. baumannii</i> <i>P. aeruginosa</i>	1/8	Lung CA, Perforated esophagus	N/N	Failure/ Indeterminate	Sepsis/ Inoperable esophageal perforation
HAP	<i>A. baumannii</i> <i>K. pneumoniae</i>	1/4	Dementia, GI bleed, CRF	N/N	Failure/ Indeterminate	Pneumonia/ GI bleed
VAP	<i>A. baumannii</i>	0.25/4	56% burns, Smoke inhalation, Hemodialysis	Y/N	Failure/ Persistence	Sepsis/ BSI with <i>Candida</i> <i>glabrata</i>
VAP	<i>S. maltophilia</i>	0.06/0.25	Age: 84, New stroke and ventilated, Pneumonia, AKI	Y/N	Failure/ Indeterminate	Septic shock, Cardiac arrest/

# Patient #31 (FDA Patient #22): HAP due to CR *A. baumannii*, *K. pneumoniae*, *P. aeruginosa* Chronic Kidney Disease, Dementia, Alzheimer Disease, Diabetes



CR <i>A. baumannii</i>			
CFDC	1	CFPM	>16
IPM	32	CPFX	>4
MEPM	32	CAZ/AVI	32
CST	1	CEF/TAZ	32
AMK	32	TGC	1
AZT	>32		

<i>K. pneumoniae</i>			
CFDC	UNK	CFPM	UNK
IPM	UNK	CPFX	UNK
MEPM	UNK	CAZ/AVI	UNK
CST	UNK	CEF/TAZ	UNK
AMK	UNK	TGC	UNK
AZT	UNK		

<i>P. aeruginosa</i>			
CFDC	UNK	CFPM	UNK
IPM	UNK	CPFX	UNK
MEPM	UNK	CAZ/AVI	UNK
CST	UNK	CEF/TAZ	UNK
AMK	UNK	TGC	UNK
AZT	UNK		

# High Stability to Various Beta-lactamase

## No Hydrolysis of Cefiderocol

Class A		Class C	Class D		
KPC-3	CTX-M-15	AmpC	OXA-23	OXA-40	OXA-48

## Relatively Low Hydrolysis of Cefiderocol

	Class B			
	IMP-1	VIM-2	L1	NDM-1
Cefiderocol	0.23	0.28	0.38	18.0
Meropenem	100	100	100	100

# List of Cefiderocol Non-susceptible Clinical Isolates SIDERO-WT-2014 to 2016

Number of Non-susceptible Strains ( $\geq 8$ $\mu\text{g/mL}$ ) from Multi-national Surveillance Studies				
Species	WT-2014	WT-2015	WT-2016	Total
<i>A. baumannii</i> /Acinetobacter spp.	28	35	65	128
<i>P. aeruginosa</i>	1	1		2
<i>S. maltophilia</i>		2		2
<i>B. cepacia</i> /multivorance	1	5	1	7
<i>K. pneumoniae</i>	6		4	10
<i>E. cloacae</i>		2		2
<i>E. aerogenes</i>	1			1
<i>S. marcescens</i>	2	2		4
<i>C. freundii</i> /koseri		2		2
<i>E. coli</i>		2		2
<i>P. mirabilis</i>			1	1
Cefiderocol non-susceptible strains	39	51	70	160
(Non-susceptible/Total, %)	(0.4%)	(0.6%)	(0.7%)	(0.6%)
Total strains	9205	8954	10470	28629

# Profile of Cefiderocol Non-susceptible Isolates

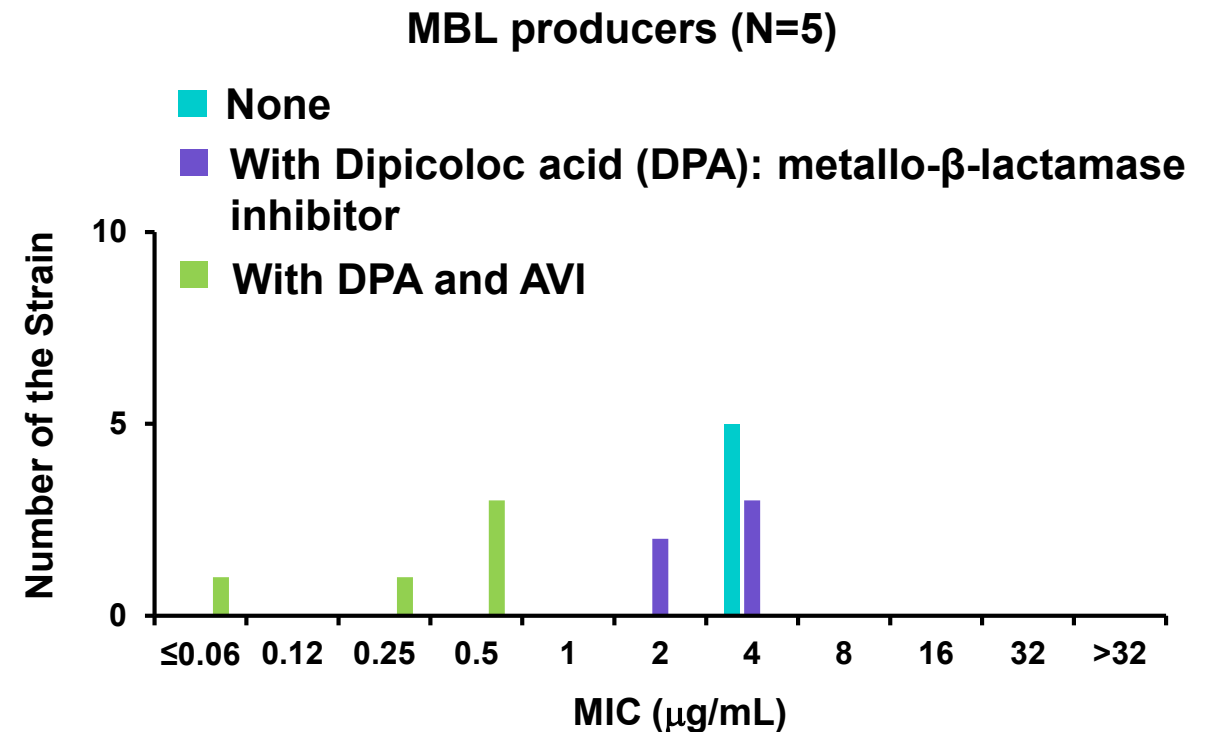
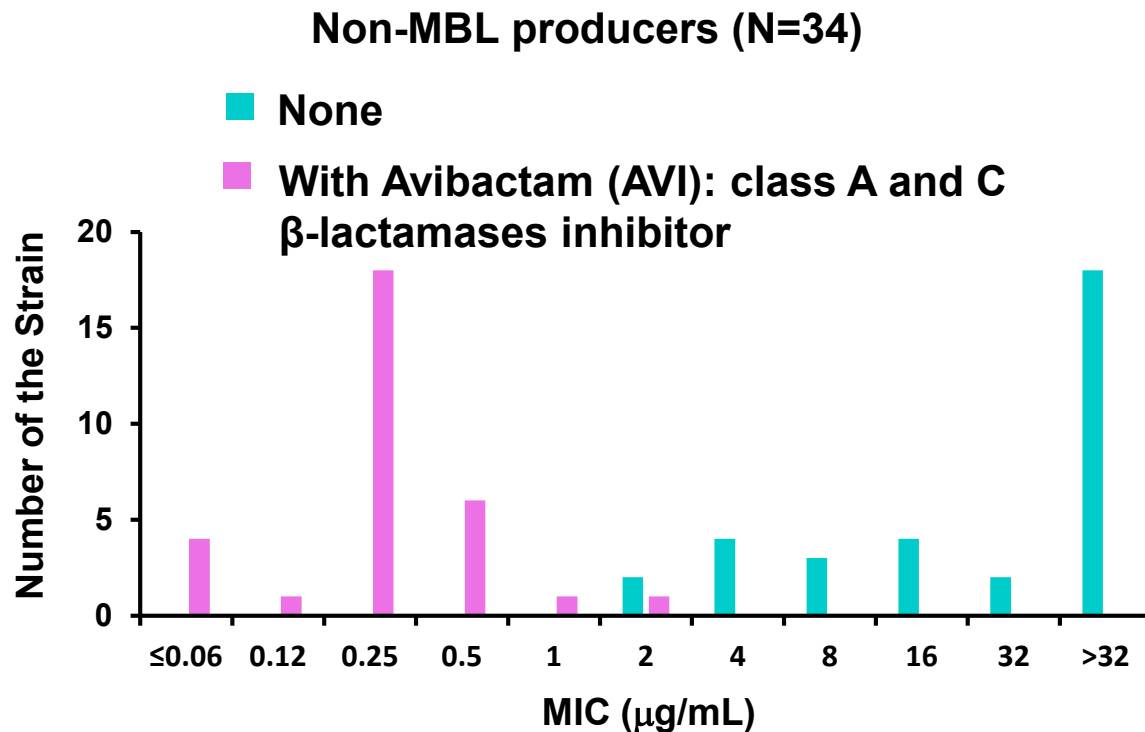
## SIDERO-WT-2014

Bacterial Species	Number of Isolates	
Enterobacteriaceae		
NDM producing <i>K. pneumoniae</i>	5	5 from Turkey
Non-NDM producing Enterobacteriaceae	4	Each 1 from USA, Italy, Germany, and Turkey
Non-fermenters		
PER producing <i>A. baumannii</i>	25	18 from Russia, 6 from Turkey, 1 from Sweden
Non-PER producing <i>A. baumannii</i>	3	3 from USA
Non-PER producing <i>P. aeruginosa</i>	1	1 from Canada
Non-PER producing <i>Burkholderia</i>	1	1 from USA

# Profile of Cefiderocol Non-susceptible Isolates

## SIDERO-WT-2014

- **All cefiderocol non-susceptible isolates were susceptible in the presence of  $\beta$ -lactamase inhibitors**
  - The cefiderocol non-susceptible of non-MBL producers including PER producing *A. baumannii* was due to serine-type  $\beta$ -lactamases
  - The cefiderocol non-susceptible of NDM producing *K. pneumoniae* was due to both of serine-type and metallo-type  $\beta$ -lactamases



# Country Enrollment in the cUTI Study

Country	Number of Study Sites	Enrollment Safety (Micro-ITT)
Bulgaria	4	23 (18)
Croatia	4	37 (36)
Czech Republic	4	36 (31)
Georgia	3	20 (16)
Germany	4	5 (2)
Hungary	4	26 (19)
Italy	4	9 (9)
Japan	6	15 (13)
Latvia	4	11 (7)
Poland	10	71 (64)
Romania	7	112 (89)
Russia	9	74 (60)
Spain	1	2 (2)
US	2	7 (5)

# Patient Demographics and Baseline Characteristics

## APEKS-NP Study (ITT Population)

Baseline Characteristics Statistic/Category	Cefiderocol N=148	Meropenem N=150
Gender (Male)	101 (68.2)	104 (69.3)
Age (Mean)	64.7	65.6
≥75 years	40 (27.0)	47 (31.3)
<75 years	108 (73.0)	103 (68.7)
<65 years	65 (43.9)	58 (38.7)
Race		
White	102 (68.9)	100 (66.7)
Asian	44 (29.7)	44 (29.3)
Other	2 (1.4)	4 (2.7)
Region		
Europe	99 (66.9)	100 (66.7)
Asia-Pacific	43 (29.1)	44 (29.3)
North America	6 (4.1)	6 (4.0)

# Enrollment by Country

## CREDIBLE-CR (Safety Population)

Country	Cefiderocol N=101 n (%)	BAT N=49 n (%)
ISR	24 (23.8)	12 (24.5)
KOR	13 (12.9)	8 (16.3)
TUR	11 (10.9)	6 (12.2)
TWN	11 (10.9)	3 (6.1)
ESP	10 (9.9)	4 (8.2)
GRC	6 (5.9)	5 (10.2)
USA	6 (5.9)	3 (6.1)
GTM	6 (5.9)	2 (4.1)
THA	4 (4.0)	2 (4.1)
BRA	3 (3.0)	2 (4.1)
HRV	3 (3.0)	0
FRA	2 (2.0)	1 (2.0)
JPN	1 (1.0)	1 (2.0)
ITA	1 (1.0)	0

# 49-Day Mortality Rates by Pathogen

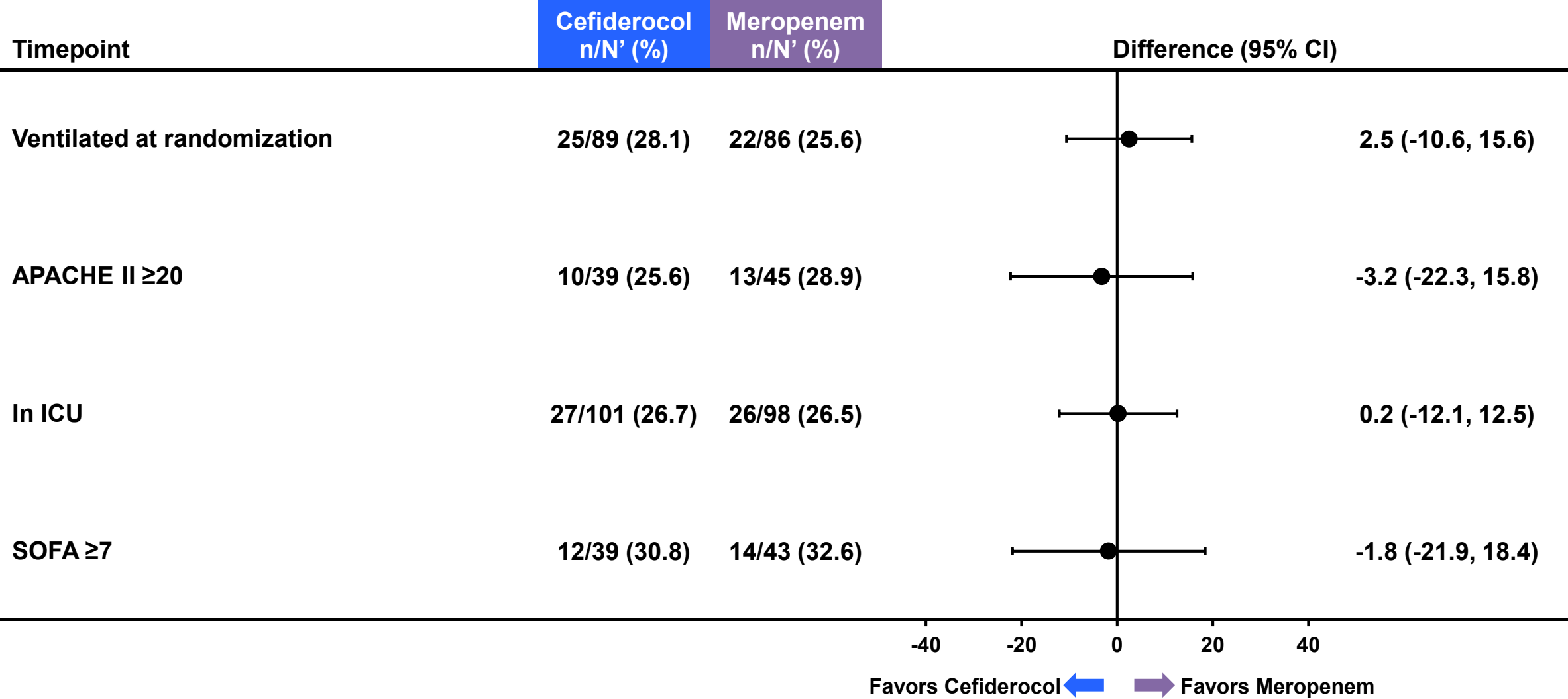
## CREDIBLE-CR Study (Safety Population)

	Cefiderocol n/N (%)	BAT n/N (%)
<b><i>Acinetobacter</i> spp.<sup>1</sup></b>	<b>21/42 (50.0)</b>	<b>4/17 (23.5)</b>
<b><i>A. baumannii</i></b>	<b>19/39 (48.7)</b>	<b>4/17 (23.5)</b>
<b><i>P. aeruginosa</i></b>	<b>6/17 (35.3)</b>	<b>2/12 (16.7)</b>
<b><i>P. aeruginosa</i> without <i>Acinetobacter</i> spp.</b>	<b>2/11 (18.2)</b>	<b>2/11 (18.2)</b>
<b><i>K. pneumoniae</i></b>	<b>8/34 (23.5)</b>	<b>4/16 (25.0)</b>
<b><i>K. pneumoniae</i> without <i>Acinetobacter</i> spp.</b>	<b>6/28 (21.4)</b>	<b>4/15 (26.7)</b>

1. *Acinetobacter* spp. includes *A. baumannii*, *A. nosocomialis* and *A. radioresistence*

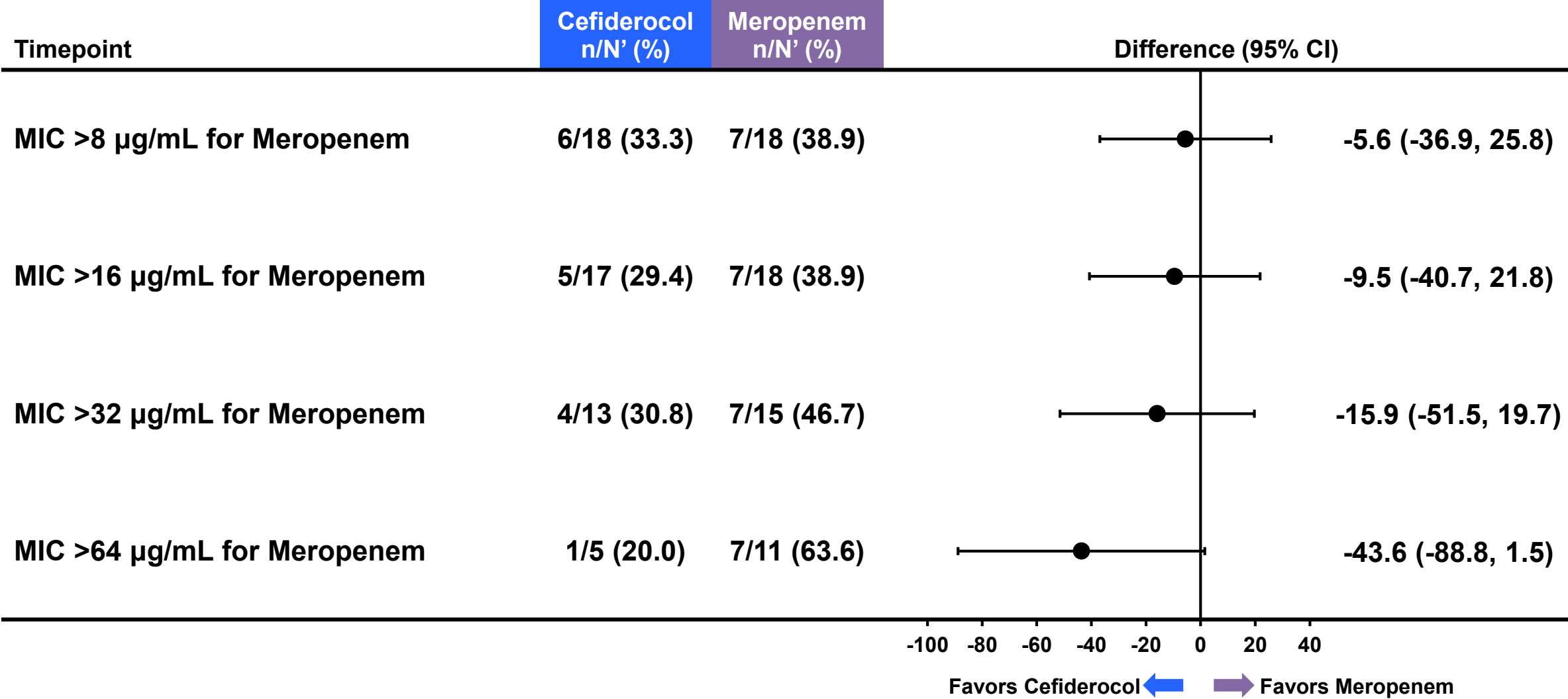
# All-cause Mortality at Day 28 in Severe Patients

## APEKS-NP Study (Safety Population)



# Comparison of ACM at Day 28 by MIC Values *Acinetobacter* spp.

APEKS-NP Study (Modified-ITT Population)



# 28-Day All-cause Mortality Rates in Recently Completed Acinetobacter-Focused Studies

